UNIVERSIDADE FEDERAL DO PARANÁ

NATÁLIA NACHBAR HUPALOWSKI

PERFIL ALIMENTAR EM PACIENTES COM ACROMEGALIA E SUA INFLUÊNCIA NO SISTEMA MUSCULOESQUELÉTICO

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Orientadora: Profª. Drª. Victória Zeghbi Cochenski Borba

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RESUMO

A acromegalia é uma doença crônica e insidiosa, geralmente causada por um adenoma hipofisário secretor do hormônio do crescimento (GH) e do fator de crescimento semelhante à insulina 1 (IGF-1). Embora o IGF-1 exerça efeitos anabólicos nos tecidos musculares e ósseos, a desregulação hormonal característica frequentemente resulta em impactos prejudiciais à saúde musculoesquelética. Os nutrientes desempenham um papel relevante nesse sistema. Minerais como cálcio, magnésio e fósforo são essenciais para a mineralização óssea e manutenção da densidade mineral óssea (DMO), enquanto proteínas e aminoácidos contribuem para preservar e aumentar a massa muscular ao estimular a síntese proteica. Além disso, vitaminas e compostos bioativos também podem beneficiar o sistema musculoesquelético. Assim, o objetivo deste estudo foi avaliar o perfil alimentar no sistema musculoesquelético em pacientes com acromegalia. Foi um estudo observacional transversal com pacientes portadores de acromegalia em acompanhamento no Serviço de Endocrinologia e Metabologia do Hospital de Clínicas da Universidade Federal do Paraná (SEMPR). A ingestão alimentar foi avaliada por um questionário de frequência alimentar (QFA) e as recomendações diárias baseadas no *Dietary Reference Intakes* (DRIs) e nos *guidelines* mais recentes da organização mundial de saúde. A DMO, a qualidade óssea, o escore ósseo trabecular (TBS), a composição corporal [massa magra total (MMT) e a massa magra apendicular (ALM)], foram medidas por absorciometria por raios-X de dupla energia (DXA). O histórico de fraturas foi capturado por questionário. Testes de força e desempenho físico foram realizados por todos os participantes. Foram incluídos 82 indivíduos, 41 no grupo com acromegalia (GA) (58,5% mulheres, média de idade de 55,9 ± 11,8 anos; Índice de massa corporal (IMC) médio de 31,14 ± 5,16 kg/m²) e 41 no grupo controle (GC) (58,5% mulheres, média de idade de 56,8 ± 14,3 anos; IMC médio de 25,5 ± 3,3 kg/m²). A média de idade ao diagnóstico da doença foi de 43,7 ± 13,0 anos, e 63,4% dos pacientes do GA apresentavam doença controlada. Em ambos os grupos, foi observada ingestão insuficiente em relação às recomendações dietéticas de nutrientes essenciais (fibras, ômega-3 e 6, vitaminas A e E, e minerais como magnésio, potássio e cálcio). No entanto, o GA apresentou maior consumo de carboidratos, gorduras trans e certos micronutrientes em comparação ao GC ($p<0,05$). Apesar de valores de DMO semelhantes, o GA apresentou maior número de fraturas (GA 0,63 ± 1,11 vs. GC 0,14 ± 0,43; p=0,001) e pior TBS (homens: GA 1,10 ± 0,43 vs. GC 1,43 ± 0,09; p=0,006; mulheres: GA 1,03 ± 0,54 vs. GC 1,35 ± 0,14; p=0,009). No GA, as fraturas foram negativamente associadas às flavonas e vitamina A e positivamente associadas aos níveis de IGF-1 ($p<0,05$ para todas as associações). A DMO e o TBS apresentaram correlações positivas com diferentes compostos bioativos com atividade anti-inflamatória (flavonas, antocianinas e betacaroteno), além de macro e micronutrientes. O GA apresentou maior massa magra total em kg (homens: GA 66,7 ± 8,9 vs. GC 52,3 ± 8,6; $p<0,001$; mulheres: GA 47,1 ± 9,1 vc. GC 38,7 ± 6,0; p=0,001), ALM em kg (homens: GA 27,7 ± 4,3 vs. GC 22,3 ± 3,1; $p<0,001$; mulheres: GA 16,9 ± 6,4 vs. GC 15,0 ± 2,4; P=0,009) em comparação ao GC. Contudo, o GA demonstrou pior desempenho nos testes TUG (s) (GA 12,22 ± 4,27 vs. GC 9,4 ± 2,7; p=0,001), TSL5 (s) (GA 16,6 ± 5,3 vs. GC 12,2 ± 2,5; $p<0,001$), VM4 (m/s) (GA 0,91 ± 0,3 vs. GC 1,16 ± 0,2; $p<0,001$) e SPPB (GA 9,0 ± 2,6 vs. GC 11,8 ± 0,5; $p<0,001$). Indivíduos com acromegalia apresentaram baixa qualidade óssea e maior prevalência de fraturas, mesmo com massa óssea adequada. A ingestão insuficiente

de compostos antioxidantes e anti-inflamatórios, aliada ao consumo excessivo de gorduras trans e carboidratos de baixa qualidade, pode ter contribuído para a piora da qualidade óssea e do desempenho físico. Apesar do impacto positivo de nutrientes como selênio, β-caroteno, flavonoides, vitamina E e niacina, esses benefícios não foram suficientes para mitigar os prejuízos, destacando os desafios complexos da acromegalia para a saúde musculoesquelética.

Palavras-chave: acromegalia; nutrição; densidade mineral óssea; massa magra.

ABSTRACT

Acromegaly is a chronic and insidious disease, usually caused by a growth hormone (GH)-secreting pituitary adenoma and insulin-like growth factor 1 (IGF-1). Although IGF-1 exerts anabolic effects on muscle and bone tissues, the characteristic hormonal dysregulation often results in detrimental impacts on musculoskeletal health. Nutrients play a significant role in this system. Minerals such as calcium, magnesium, and phosphorus are essential for bone mineralization and the maintenance of bone mineral density (BMD), while proteins and amino acids contribute to preserving and increasing muscle mass by stimulating protein synthesis. Additionally, vitamins and bioactive compounds can also benefit the musculoskeletal system. Thus, the objective of this study was to evaluate the impact of dietary intake on the musculoskeletal system in patients with acromegaly. This was a cross-sectional observational study with patients diagnosed with acromegaly under follow-up at the Endocrinology and Metabolism Service of the Clinical Hospital of the Federal University of Paraná (SEMPR). Dietary intake was assessed using a food frequency questionnaire (FFQ), and daily recommendations were based on the Dietary Reference Intakes (DRIs) and the latest World Health Organization guidelines. BMD, bone quality, trabecular bone score (TBS), body composition [total lean mass (TLM) and appendicular lean mass (ALM)] were measured by dual-energy X-ray absorptiometry (DXA). Fracture history was captured through a questionnaire. Strength and physical performance tests were performed by all participants. A total of 82 individuals were included, 41 in the acromegaly group (AG) (58.5% women, mean age 55.9 ± 11.8 years; mean body mass index (BMI) 31.14 ± 5.16 kg/m²) and 41 in the control group (CG) (58.5% women, mean age 56.8 ± 14.3 years; mean BMI 25.5 ± 3.3 kg/m²). The mean age at disease diagnosis was 43.7 ± 13.0 years, and 63.4% of AG patients had controlled disease. In both groups, insufficient intake of essential nutrients (fiber, omega-3 and 6, vitamins A and E, and minerals such as magnesium, potassium, and calcium) was observed relative to dietary recommendations. However, the AG showed higher intake of carbohydrates, trans fats, and certain micronutrients compared to the CG ($p<0.05$). Despite similar BMD values, the AG had a higher number of fractures (AG 0.63 ± 1.11 vs. CG 0.14 ± 0.43; $p=0.001$) and worse TBS (men: AG 1.10 ± 0.43 vs. CG 1.43 ± 0.09; $p=0.006$; women: AG 1.03 ± 0.54 vs. CG 1.35 ± 0.14; $p=0.009$). In the AG, fractures were negatively associated with flavones and vitamin A and positively associated with IGF-1 levels ($p<0.05$ for all associations). BMD and TBS showed positive correlations with different bioactive compounds with anti-inflammatory activity (flavones, anthocyanins, and beta-carotene), as well as macro and micronutrients. The AG presented higher total lean mass in kg (men: AG 66.7 ± 8.9 vs. CG 52.3 ± 8.6; $p<0.001$; women: AG 47.1 ± 9.1 vs. CG 38.7 ± 6.0; $p=0.001$) and ALM in kg (men: AG 27.7 ± 4.3 vs. CG 22.3 ± 3.1; $p<0.001$; women: AG 16.9 ± 6.4 vs. CG 15.0 ± 2.4; $p=0.009$) compared to the CG. However, the AG demonstrated worse performance in TUG tests (s) (AG 12.22 ± 4.27 vs. CG 9.4 ± 2.7; $p=0.001$), TSL5 (s) (AG 16.6 ± 5.3 vs. CG 12.2 ± 2.5; $p<0.001$), VM4 (m/s) (AG 0.91 ± 0.3 vs. CG 1.16 ± 0.2; $p<0.001$), and SPPB (AG 9.0 ± 2.6 vs. CG 11.8 ± 0.5; $p<0.001$). Individuals with acromegaly presented poor bone quality and a higher prevalence of fractures, even with adequate bone mass. The insufficient intake of antioxidant and anti-inflammatory compounds, combined with excessive consumption of trans fats and low-quality carbohydrates, may have contributed to the worsening of bone quality and physical performance. Despite the positive impact of nutrients such as selenium, β-carotene, flavonoids, vitamin E, and

niacin, these benefits were not sufficient to mitigate the impairments, highlighting the complex challenges of acromegaly for musculoskeletal health.

Keywords: acromegaly; nutrition; bone mineral density; lean mass.

LISTA DE TABELAS

LISTA DE ABREVIATURAS OU SIGLAS

AA	Ácido Araquidônico
AG	Acromegaly group
CG	Control group
DCNT	Doenças crônicas não transmissíveis
DCV	Doenças Cardiovasculares
DHA	Ácido docosahexaenoico
DMO	Densidade Mineral Óssea
DRI	*Dietary Reference Intakes*
DXA	Densitometria por dupla emissão de raio X
EPA	Ácido eicosapentainoico
FPP	Força de Preensão Palmar
FRAX	Ferramenta de Avaliação do Risco de Fratura
g	Gramas
GA	Grupo Acromegalia
GC	Grupo Controle
GH	*Growth Hormone*
GS	*Gait Speed Test*
IGF-1	*Insulin-like Growth Factor 1*
IID	Índice Inflamatório da Dieta
IL-6	Interleucina-6
IMC	Índice de Massa Corporal
Kcal	quilocalorias
m²	metros quadrados
mcg	microgramas
mg	miligramas
MMT	Massa magra total
ND	Não definido
NFkB	Fator Nuclear Kappa B
p	valor de p
PCR	Proteína C reativa
QFA	Questionário de Frequência Alimentar
RDA	*Recommended Dietary Allowance*

s.d	Sem data
SEMPR	Serviço de Endocrinologia e Metabologia do Hospital de Clínicas da Universidade Federal do Paraná
SPPB	*Short Physical Performance Battery*
SPSS	*Statistical Package for the Social Science*
STS	*Sit to Stand Test*
TBS	*Trabecular Bone Score*
TCLE	Termo de Consentimento Livre e Esclarecido
TLM	*Total Lean Mass*
TNF-α	Fator de necrose tumoral alfa
TSL	Teste de sentar-se e levantar
TUG	*Time Up and Go*
WHO	*World Health Organization*
ω-3	Ômega-3
ω-6	Ômega-6

LISTA DE SÍMBOLOS

ω – Ômega

p – valor de p

α - alfa

SUMÁRIO

1 INTRODUÇÃO

Este estudo integra o projeto ACROSSO, que realizou uma avaliação abrangente do sistema musculoesquelético e do perfil alimentar em pacientes com acromegalia. A proposta central foi explorar como a ingestão alimentar pode influenciar a composição corporal, força muscular, densidade e qualidade óssea, oferecendo uma perspectiva integrada sobre os acometimentos enfrentados por esses pacientes em decorrência da doença.

A acromegalia é uma doença crônica, rara e progressiva, resultante, na maioria dos casos, de um adenoma hipofisário produtor de hormônio do crescimento (GH). O excesso de GH eleva os níveis do fator de crescimento semelhante à insulina tipo 1 (IGF-1), um mediador anabólico que atua em tecidos musculares e ósseos, além de regular processos metabólicos essenciais (BOLANOWSKI, 2022; XIAO, 2023). Embora sua hiperatividade proporcione ganhos estruturais em massa muscular e óssea, ela também desencadeia alterações metabólicas e funcionais que comprometem a qualidade de vida dos pacientes (SLAGBOOM, 2023).

Os impactos musculares da acromegalia são paradoxais. Apesar do aumento da massa muscular, frequentemente observado devido ao estímulo anabólico do GH e IGF-1, muitos pacientes relatam fraqueza muscular proximal. Essa condição, possivelmente associada à disfunção na sinalização da insulina e à ativação inadequada dos receptores de GH, compromete a funcionalidade muscular e pode dificultar atividades cotidianas (FÜCHTBAUER et al., 2017; ARLIEN-SOBORG et al., 2022). Além disso, alterações no metabolismo de aminoácidos e ácidos graxos sugerem uma tendência à lipólise e ao anabolismo proteico, configurando um cenário metabólico distinto nesses indivíduos (ARLIEN-SOBORG et al., 2022).

No tecido ósseo, a acromegalia promove remodelação óssea acelerada devido à hiperatividade do GH e IGF-1. Esse processo afeta tanto os ossos trabeculares, quanto os corticais (GIUSTINA, 2023), levando a alterações na microarquitetura óssea e aumentando o risco de fraturas (MAZZIOTTI et. al., 2015; SOROHAN & POIAN, 2022), mesmo na presença de densidade mineral óssea (DMO) aparentemente normal (BIOLETTO et. al., 2023). Fraturas vertebrais são particularmente comuns, destacando a discrepância entre a densidade e a qualidade do osso (MAZZIOTTI et al., 2015). Assim, a avaliação do osso vai além da DMO,

exigindo métodos que também considerem parâmetros qualitativos como o escore do osso trabecular, do Inglês *Trabecular Bone Score* (TBS), geralmente mais baixo em pacientes com acromegalia, indicando uma qualidade óssea comprometida (BIOLETTO et. al., 2023).

O perfil alimentar pode ser um aspecto essencial no manejo da doença, pois nutrientes específicos exercem influência direta na saúde musculoesquelética. Proteínas ingeridas em quantidades adequadas são fundamentais para a manutenção da massa muscular, já que estimula diretamente a sua síntese (GANAPATHY & NIEVES, 2020; BIRD et al., 2024), enquanto cálcio, vitamina D, magnésio e outros micronutrientes desempenham papéis cruciais na remodelação e qualidade óssea (VANUCCI et. al., 2018; QIAO et. al., 2020; LIU et. al., 2024). Uma alimentação desequilibrada pode agravar os efeitos deletérios da acromegalia, contribuindo para alterações no metabolismo energético, redução da força muscular e fragilidade óssea. Enquanto a ingestão dos alimentos com nutrientes específicos pode contribuir positivamente para o curso da doença, favorecendo a prevenção ou minimização dos danos decorrentes do excesso de GH e IGF-1.

Até o presente momento, não existem estudos na literatura que explorem a qualidade alimentar em pacientes com acromegalia, seja em relação ao impacto dos nutrientes na composição corporal e força muscular, seja na densidade e qualidade óssea desse público.

1.1 OBJETIVOS

1.1.1 Objetivo geral

Avaliar o perfil alimentar em pacientes com acromegalia.

1.1.2 Objetivos específicos

Avaliar em pacientes com acromegalia a influência do perfil alimentar no sistema musculoesquelético, mais especificamente na:

- Densidade óssea, qualidade óssea e fraturas;
- Força, desempenho muscular e composição corporal.

2 REVISÃO DE LITERATURA

2.1 CARACTERÍSTICAS DA DOENÇA E EPIDEMIOLOGIA

A acromegalia é uma doença rara e insidiosa comumente causada por um adenoma hipofisário, produtor de GH, resultando em concentrações elevadas de GH e de IGF-1 (GIUSTINA et. al., 2008).

Embora subdiagnosticada, a acromegalia apresenta incidência semelhante entre os sexos e pode ocorrer em qualquer faixa etária, sendo mais frequentemente diagnosticada entre a quarta e quinta décadas de vida. A prevalência é estimada entre 40 e 70 casos por milhão de habitantes, com uma taxa de incidência anual de aproximadamente 5,9 novos casos por 100.000 pessoas (CRISAFULLI et. al., 2021). A expectativa de vida dos pacientes com acromegalia é reduzida em cerca de 10 anos em comparação com a população geral (MAFFEZZONI et al., 2016).

Até pouco tempo, o diagnóstico da doença costumava ser mais tardio, levando em torno de 8 a 10 anos, com as mulheres tendo um atraso no diagnóstico relativamente maior que os homens por seus sintomas menos específicos (ROSENDAL et. al., 2024), sendo, muitas vezes, acompanhado de fácies característica, como macroglossia, macrognatia, crescimento de extremidades, doenças metabólicas, como diabetes mellitus 2, hipertensão, alguns tipos de cânceres e hipopituitarismo, além de alterações hormonais e musculoesqueléticas, muitas vezes presentes no momento do diagnóstico (ELBAUM, et. al., 2023; MERCADO & RAMÍREZ-RENTERÍA, 2018). Porém, com os avanços na tecnologia e uso de exames de imagens, o diagnóstico vem sendo mais precoce (ROSENDAL et. al., 2024).

2.2 MASSA E QUALIDADE ÓSSEA

O GH e o IGF-1 são importantes reguladores da homeostase óssea e da cartilagem (GIUSTINA et. al., 2008), desempenhando um papel central na obtenção do crescimento ósseo longitudinal normal e na massa óssea (MAZZIOTI et. al., 2015). O GH estimula a proliferação de células da linhagem osteoblástica e interfere no destino dos precursores mesenquimais favoráveis à osteoblastogênese e condrogênese em oposição à adipogênese. Além de seus efeitos na diferenciação dos osteoblastos, o GH estimula, direta ou indiretamente através do IGF-1, as funções do osteoblasto maduro. O GH também estimula a carboxilação da

osteocalcina, um marcador da função osteoblástica e favorece o acúmulo de osteoprotegerina na matriz óssea (LIM et. al., 2015). É clinicamente relevante que tanto a deficiência de GH quanto o excesso possam afetar a saúde do osso, diminuindo ou estimulando excessivamente a remodelação desse tecido (KAMENICKI et. al., 2014).

Uma metanálise com 1935 pacientes com acromegalia demonstrou que os indivíduos com a doença apresentaram maior formação e reabsorção óssea em comparação aos indivíduos controle, sem diferenças significativas na DMO entre os grupos. Também foi vista uma alta prevalência de fraturas vertebrais até três vezes maior em pacientes com a doença ativa comparados àqueles com doença controlada (MAZZIOTI et. al., 2015).

O TBS é um índice utilizado para avaliar a microarquitetura óssea, derivado da análise de imagens da coluna lombar obtidas durante o exame DXA. Estudos sugerem que o TBS significativamente reduzido em pacientes com acromegalia, quando comparados a controles, poderia explicar a alta incidência de fragilidade neste público (HONG et. al., 2016; CALATAYUD et. al., 2021). No estudo de Hong e colaboradores, o TBS da coluna lombar foi menor nos pacientes com acromegalia em comparação aos controles de ambos os sexos, apesar da DMO ter sido semelhante entre os grupos. Pacientes com acromegalia e com hipogonadismo associado apresentaram menores valores de TBS em relação a controles tanto em homens quanto em mulheres, embora a DMO em todos os locais tenha sido similar para os dois grupos (HONG et. al., 2016). A redução da qualidade óssea é o principal fator associado ao elevado risco de fraturas observado nesse grupo populacional, com uma razão de chances de 8,26 em comparação aos controles, predominantemente envolvendo fraturas vertebrais (MAZZIOTI et al., 2015). De forma consistente, Uygur et al. identificaram uma alta prevalência de fraturas vertebrais em pacientes com acromegalia, correspondendo a 72,9%, em contraste com 20% nos controles (UYGUR et. al., 2021). O mecanismo por trás desse risco aumentado é em decorrência da renovação óssea, alterações na microarquitetura e presença de hipogonadismo (RIBEIRO de MOURA et. al., 2022).

2.3 COMPOSIÇÃO CORPORAL E DESEMPENHO FÍSICO

A composição corporal também está alterada nos pacientes com acromegalia, com diminuição da gordura corporal total, aumento da massa muscular esquelética e da água corporal total (FREDA et. al., 2009). O mecanismo de ação do GH no músculo esquelético ocorre direta e indiretamente via IGF-I. As vias moleculares que levam à hipertrofia muscular pelo aumento da síntese proteica sem alterações na proteólise, são bem estudadas em animais e humanos. Também está bem documentado que a reposição de GH em adultos com deficiência deste hormônio leva ao aumento da massa muscular poucos meses após o tratamento, embora o efeito sobre a força muscular seja menos claro ou atrasado (CUNEO, 1991).

Pacientes com acromegalia podem apresentar fraqueza muscular proximal no diagnóstico e durante o seguimento a longo prazo. A força de preensão palmar (FPP) reduzida antes do tratamento normalizou após o mesmo (FÜCHTABAUER et. al., 2017). Outro estudo com pacientes com acromegalia acima de 60 anos, demonstrou redução da força de preensão palmar, porém os testes de desempenho físico, como a velocidade da marcha de 4 metros e a presença de sarcopenia não foram diferentes dos controles (HATIPOGLU et. al., 2015). Além disso, em uma série de 17 pacientes com acromegalia avaliados para disfunção neuromuscular, 9 tinham evidência de miopatia no início do estudo que persistiu em menor intensidade até 1 ano após cirurgia hipofisária bem-sucedida (KATZNELSON, 2009). Esses dados sugerem que a acromegalia resulta em mudanças na função do músculo esquelético que não se correlacionam claramente com o grau de aumento da massa magra e síntese de proteínas. A deposição de tecido adiposo intramuscular está aumentada nesses pacientes e potencialmente parece ser um dos maiores contribuintes para a resistência insulínica que ocorre neste público, contribuindo para uma maior morbidade e mortalidade cardiovascular (REID et. al., 2015).

2.4 IMPACTO DO PERFIL ALIMENTAR

Atualmente, não existem estudos na literatura que avaliem especificamente a alimentação ou a qualidade alimentar de indivíduos com acromegalia. Apenas um estudo foi conduzido por Coopmans et. al. para avaliar o impacto de uma dieta cetogênica em 11 indivíduos com acromegalia durante um período de duas

semanas. Após o período, foi verificada a diminuição do IGF-1 em 10 dos participantes. Outros parâmetros não foram avaliados (COOPMANS et. al., 2020).

É amplamente reconhecido que os nutrientes desempenham um papel fundamental na qualidade de vida, no desempenho físico, na saúde óssea e na prevenção de doenças crônicas não transmissíveis (DCNT). Padrões alimentares inadequados podem contribuir para um estado inflamatório de baixo grau, o que não só predispõe ao desenvolvimento de DCNT, como também impacta negativamente na massa óssea (JACKSON et al., 2023) e na massa muscular (SAKUMA et. al., 2015).

A composição dietética pode modular esse estado inflamatório do organismo, influenciando diretamente os níveis de marcadores inflamatórios, como proteína-C reativa (PCR), interleucina-6 (IL-6) e fator de necrose tumoral alfa (TNF-α). Tais marcadores inflamatórios têm sido associados a uma redução na DMO (DING et al., 2015), indicando que a dieta pode desempenhar um papel crucial na modulação do estado inflamatório sistêmico e, consequentemente, na saúde musculoesquelética.

Ademais, alguns nutrientes são particularmente cruciais para a formação e manutenção do tecido ósseo, incluindo vitamina D, cálcio e magnésio (SHI et al., 2020). Além desses nutrientes, padrões alimentares que incluem maior consumo de frutas, verduras, legumes, cereais integrais, leite e derivados mostram uma associação positiva com a DMO. Em contraste, dietas ricas em alimentos açucarados, carnes vermelhas e cafeína estão associadas a um impacto negativo (De JONGE et al., 2015).

Um estado inflamatório de baixo grau também pode repercutir de forma negativa na massa muscular, apresentando prejuízo no metabolismo do músculo esquelético através do favorecimento do catabolismo (SAKUMA et. al., 2015). Um estudo publicado em 2006 concluiu que concentrações séricas mais elevadas de IL-6 e PCR contribuíram para um risco aumentado de redução da força muscular (SCHAAP et. al., 2006), além disso, em doenças como câncer, doença pulmonar obstrutiva crônica, síndrome da imunodeficiência adquirida e insuficiência cardíaca, a inflamação sistêmica foi responsável por mediar a perda de massa muscular (SAKUMA et. al., 2015).

Por isso, estudar a ingestão alimentar nesse público associada a todos os fatores supracitados é importante, pois os benefícios trazidos através de uma boa

alimentação podem ser fundamentais para o controle da doença, de sua progressão e melhora da qualidade de vida dos portadores.

3. ARTIGOS

Esta seção apresenta os dois artigos desenvolvidos ao longo do mestrado. O artigo 1 foi submetido à revista Clinical Nutrition (ESPEN) e apresenta-se no formato solicitado pela revista.

ARTIGO 1: Revista: Clinical Nutrition (ESPEN)

Impact of Dietary Intake on Bone Mineral Density and Bone Quality in Patients with Acromegaly

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ABSTRACT

Background & Aims: Nutrition plays a critical role in maintaining bone health, excessive secretion of growth hormone (GH) and insulin-like growth factor 1 (IGF-1), in patients with acromegaly has been associated with disrupting bone remodeling and increased risk of vertebral fractures. The aim of this study was to assess the dietary intake profile of patients with acromegaly and its impact on bone density, quality and fractures. **Methods:** cross-sectional, observational, controlled study which included individuals with acromegaly (AG) and matched controls by sex and age (CG). Food intake was evaluated by a food frequency questionnaire (FFQ) and dietary reference intakes (DRIs). Bone mineral density (BMD) and bone quality [trabecular bone score (TBS) measured by dual-energy X-ray absorptiometry (DXA) and the history of past fractures captured by a questionnaire. **Results:** Eighty-two individuals were included, 41 in the AG (58.5% women, mean age 55.9 ± 11.8 years; mean BMI 31.14 ± 5.16) and 41 in the CG (58.5% women, 56.8 ± 14.3 years and mean BMI was 25.5 ± 3.3). The mean age at diagnosis of acromegaly was 43.7 ± 13.0 years and 63.4% of AG had a controlled disease. In both groups, insufficient intake, compared to DRIs, of essential nutrients (fiber, omega-3 and 6, vitamins A and E) and minerals (magnesium, potassium, and calcium) was observed. Compared to the CG, the AG showed a higher intake of carbohydrates, trans fats, and certain micronutrients compared to the CG, $p<0.05$ for all, similar BMD values, higher number of fractures (AG 0.63 ± 1.11 vs. CG 0.14 ± 0.43; p=0.001) and poorer TBS (men AG 1.10 ± 0.43 vs. CG1.43 ± 0.09; p=0.006; women AG 1.03 ± 0.54 vs. CG 1.35 ± 0.14; p=0,009). In the AG fractures were negatively associated to flavones and vitamin A, and positively associated to IGF-1 levels ($p<0.05$ for all). BMD and TBS were positively associated with different bioactive compounds (flavone,

anthocyanin, beta-carotene and vitamin C), macronutrients and vitamins with anti-inflammatory activity. **Conclusion:** individuals with acromegaly had low bone quality and higher prevalence of fractures despite adequate BMD associated to inadequate intake of antioxidant and anti-inflammatory compounds, combined with excessive consumption of trans fats and poor-quality carbohydrate.

Key-words: acromegaly; bone mass density; diet; nutrition; nutrient intake.

INTRODUCTION

Acromegaly is an insidious disease caused in most cases by a GH-secreting pituitary adenoma (1), which promotes excessive and prolonged tissue exposure to high levels of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) (2). This hormonal imbalance promotes excessive bone remodeling, which is not adequately compensated by bone formation, compromising the structure of both cortical and trabecular bones. Although many patients with acromegaly exhibit increased or preserved BMD, skeletal fragility, measured by trabecular bone score (TBS) and the risk of vertebral fractures remain high due to deterioration of bone microarchitecture (3, 4, 5).

Various factors influence bone health in individuals with acromegaly, such as disease activity, hypogonadism, and the presence of comorbidities, such as type 2 diabetes mellitus (4, 6). Additionally, adequate nutrient intake plays a vital role in maintaining bone health. Sufficient energy intake is necessary to support bone metabolism, as prolonged energy deficits can impair bone formation and increase bone resorption (7). Proteins, essential for maintaining muscle mass, are also important for bone health as they contribute to bone matrix formation, thereby supporting bone density (8).

Calcium, magnesium and phosphorus are the main minerals of bone matrix, crucial for bone mineralization and maintenance of bone density (9). Calcium and phosphorus absorption depends on adequate amounts of vitamin D (10, 11). Additionally, vitamin K is important for the carboxylation of osteocalcin, a key protein for calcium deposition in bones (12). Other substances such as polyphenols, especially flavonoids, also have positive effects on bone health due to their antioxidant capacity, protecting against the damage induced by reactive oxygen

species (13, 14) Moreover, they could reduce the risk of osteoporosis and bone loss, particularly in the femoral neck (15).

Studies investigating the relationship between diet and bone health in patients with acromegaly are limited. Among the few available, the study of Coopmans et al. evaluated the effects of a eucaloric ketogenic diet with very low carbohydrate intake in 11 individuals with acromegaly over two weeks, reporting a decrease in IGF-1 serum levels (16). Building on this context, our study aims to assess the dietary intake profile of patients with acromegaly and its impact on bone density, quality, and fractures.

MATHERIALS AND METHODS

This was an observational, cross-sectional study approved by the Ethics Committee of our institution under CAAE: 49629321.7.0000.0096, approval number 6.293.233) including patients with acromegaly followed at the Neuroendocrine Unit of the Endocrine Division (SEMPR) of our academic research center, which is a reference center for pituitary diseases in South of Brazil.

Patients with acromegaly of both sexes over the age of 18 were invited to participate during their routine medical appointments. All patients who agreed to participate signed an Informed Consent Form. Exclusion criteria were those with uncontrolled metabolic or chronic diseases or active malignant neoplasms; those using medications or drugs that could interfere with muscle or bone function, those with any physical impairment preventing functional physical analysis, and patients who could not do the required tests and exams.

Patients with acromegaly composed the acromegaly group (AG) and completed a standardized questionnaire about demographic data, disease characteristics, type of treatment, medications in use to control the disease and other indications, physical

activity, lifestyle habits (smoking and alcohol consumption), personal and family history of fractures, and the presence of comorbidities. Data not captured during the interview was collected from medical records. The participants were then referred for nutritional and physical evaluations (weight, height, and calculation of body mass index [BMI]) and underwent a dual-energy X-ray absorptiometry (DXA) scan.

The AG was considered to have controlled disease if the IGF-1 levels were within the normal reference range for age and sex at the moment of the study. A control group (CG), matched by sex and age, was recruited from relatives of patients and individuals from the community and underwent the same evaluations as the patients.

ANTHROPOMETRIC ASSESSMENT

Weight was measured using a calibrated anthropometric scale (Plenna®) with the participant barefoot. Height was measured using a vertical stadiometer (Tonelli Gomes®). Body mass index (BMI) was calculated by dividing the participant's weight (kg) by the squared height (meters). BMI results for participants under 60 years old were classified as underweight (BMI < 18.5 kg/m²), normal (18.6 kg/m² < BMI < 24.9 kg/m²), overweight (25.0 kg/m² < BMI < 29.9 kg/m²), obesity grade I (30.0 kg/m² < BMI < 34.9 kg/m²), obesity grade II (35 kg/m² < BMI < 39.9 kg/m²), and grade III obesity (BMI above 40 kg/m²). For participants over 60 years old, BMI was considered normal if >22 kg/m² and <27 kg/m² (17).

BONE MINERAL DENSITY (BMD)

The BMD was measured using dual-energy X-ray absorptiometry (DXA) with a Horizon A device (serial number: 201383, Hologic, Bedford, MA, USA). Lumbar spine (LS), femoral neck (FN), and total hip (TH) were evaluated, with results expressed in g/cm² and classified as either normal or low BMD based on reference values

determined by the International Society of Clinical Densitometry (ISCD) (18). The BMD of patients ≤ 50 years and premenopausal women were considered below the expected range for age or low if the Z-score was lower than -2.0 standard deviations (SD). BMD for postmenopausal women or individuals over 50 years of age was classified based on T-scores and osteopenia defined as a T-score lower than -1.0 SD and osteoporosis as a T-score equal to or less than -2.5 SD, both considered as low BMD. A lateral spine image was obtained for vertebral fracture assessment (VFA) and analyzed according to Genant's semiquantitative scale (19).

Trabecular bone score (TBS) analysis was performed using TBS Insight software version 3.0 (MediMaps, Geneva, Switzerland) based on lumbar spine images. TBS was classified as degraded when ≤ 1.23, partially degraded when > 1.23 and <1.31, and normal when ≥ 1.31 (20).

FRAX CALCULATION

Fracture risk assessment was performed for patients ≥ 40 years, using the FRAX Brazil 2.0 tool (Fracture Risk Assessment Tool) developed to estimate the 10-year risk of major osteoporotic fractures (hip, spine, forearm, or shoulder) and hip fractures specifically (21). Clinical data of patients and controls were entered into the FRAX 2.0 online calculator, available on the ABRASSO (Brazilian Association for Bone Assessment and Osteometabolism) website (https://abrasso.org.br/frax-brasil/). The calculated risk value was used to classify patients into distinct categories: low, moderate, or high.

FOOD FREQUENCY QUESTIONNAIRE (FFQ)

To assess dietary patterns and nutrient intake, a validated Food Frequency Questionnaire (FFQ) was used for the adult Brazilian population aged 18 to 60 years,

who were overweight, i.e., BMI above 25 kg/m² (22). The FFQ includes 90 foods or preparations, divided into fifteen sections: 1) foods or preparations; 2) pasta; 3) various dishes and snacks; 4) meats; 5) rice, tubers, and vegetables; 6) eggs; 7) dairy products; 8) fats; 9) cereals; 10) green leaves; 11) fruits and juices; 12) miscellaneous; 13) bread, cakes, and cookies; 14) various drinks; and 15) sweets and desserts. During the interview, the participant was asked to indicate whether they consumed the food or preparation, the frequency throughout the month, and the amount consumed in household measures or the approximate value in grams if known.

To assist in reporting quantities, photos of household measuring utensils and dishes were shown to observe and define the proportion of the plate occupied by the food, to estimate as closely as possible the amount consumed by the participant (23). FFQ data were entered into a pre-designed Excel® spreadsheet, which displayed the quantities of 38 macronutrients, micronutrients, and bioactive compounds per 100 grams of food or preparation. A formula was created to automatically calculate the quantity consumed by the patient. The calculation of dietary component intake used the Brazilian Food Composition Table (TBCA) (24), the USDA Food and Nutrient Database (25), the Brazilian table of Carotenoid Composition in Foods (26), and the Phenol-Explorer 3.0 database (27). The daily amount of required nutrients was determined by Dietary Reference Intakes (DRIs) (28) and the latest WHO guidelines on fat and carbohydrate consumption (29, 30).

STATISTICAL ANALYSIS

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 21. A descriptive analysis of the frequency distribution of all variables was conducted. The Kolmogorov-Smirnov test was used

to assess the normality of the variables in the study. To evaluate differences between means, the student's t-test was used for parametric data and the Mann-Whitney test for non-parametric data. For the evaluation of categorical data, Fisher's exact test and the chi-square test were used. Spearman's correlation was applied to correlate nutrient intake with physical performance and muscle strength to non-parametric data and Pearson's correlations with normal distribution. The classification of the degree of correlation, i.e., the strength between the variables, followed these parameters: weak when $0.31 < r < 0.5$; moderate when $0.51 < r < 0.7$; and strong when $0.71 < r < 0.9$ (30). Results with statistical significance were considered when the p-value was <0.05.

RESULTS

Throughout one year, we recruited 57 consecutive patients with acromegaly who were followed at our institution, and from this group, 8 refused to participate or presented a condition that could impact the test results. Additionally, other 8 individuals declined to answer the FFQ questionnaire and, therefore, withdrew their informed consent. In the end, 82 individuals were studied, 41 in the AG and 41 matched controls (CG).

Table 1 shows the main clinical characteristics of the study groups. Most of the participants were of white ethnicity, with a significant difference between the groups related to the presence of 6 (14.6%) Asian Brazilians in the CG versus none in the AG ($p = 0.01$). In the AG group, 58.5% were women and the mean age was 55.4 ± 11.8 years at the time of the study, with a mean age at diagnosis of the disease of 43.7 ± 13.0 years. Thirty-five (85.4%) of the AG underwent surgical treatment and 27 (65.8%) were on medical treatment with somatostatin receptor ligands (SRL), cabergoline, and/or pegvisomant. The AG had a higher BMI and higher prevalence of

hypertension, obesity, hypogonadism, diabetes, mood disorder, hypothyroidism, and hypopituitarism $p<0.05$ for all. Out of 9 male patients with hypogonadism, 4 were on testosterone hormone replacement therapy, and out of 10 women, 7 were on progesterone and estrogen replacement (Table 1).

Table 1. Clinical characteristics of the patients with acromegaly (AG) and of the control group (CG)

Characteristics	**AG (n=41)**	**CG (n=41)**	***P value***
Age (years)	55.9 ± 11.8	56.8 ± 14.3	0.77
Ethnicity			0.01
White, n (%)	38 (92.7)	34 (82.9)	
Black, n (%)	3 (7.3)	1 (2.4)	
Asian, n (%)	0 (0)	6 (14.6)	
Smoking, n (%)	7 (17.1)	1 (2.4)	0.02
Height (m)	1.66 ± 0.11	1.64 ± 0.08	0.44
Weight (Kg)	87.0 ± 18.6	70.1 ± 11.3	<0.001
Body Mass Index (kg/m²)	31.1 ± 5.2	25.5 ± 3.3	<0.001
Normal, n (%)	6 (14.6)	25 (61.0)	
Overweight, n (%)	15 (36.6)	11 (26.8)	
Obesity grade I, n (%)	10 (24.4)	5 (12.2)	
Obesity grade II, n (%)	7 (17.1)	0 (0)	
Obesity grade III, n (%)	3 (7.3)	0 (0)	
Disease data			
Time since diagnosis (years)	12.3 ± 7.8	NA	
Age at diagnosis (years)	43.7 ± 13.0	NA	
Active disease, n (%)	13 (31.7)	NA	

Serum IGF-1 levels (ng/ml)	256.6 ± 164.8	NA	
Surgical treatment, n (%)	35 (85.4)	NA	
Medications, n (%)	27 (65.8)	NA	
Somatostatin receptor ligands			
Octreotide	26 (63.4)	NA	
Lanreotide	15 (36.6)	NA	
Cabergoline	7 (17.1)	NA	
Pegvisomant	4 (9.7)	NA	
Comorbidities, n (%)			
Hypertension	23 (56.1)	14 (34.1)	0.057
Obesity	20 (48.8)	6 (14.6)	0.001
Dyslipidemia	16 (39.0)	12 (29.3)	0.390
Diabetes	15 (36.6)	3 (7.3)	0.003
Hypothyroidism	9 (21.9)	1 (2.4)	0.010
Hypogonadism	9 (21.95)	0	<0.001
Men	4 (44.4)	0	
Hormonal replacement	1 (25.0)	0	
Women	5 (55.5)	0	
Hormonal replacement	4 (80.0)	0	
Hypopituitarism	7 (17.1)	0	0.01
Mood disorder	6 (14.6)	0	0.032
Osteoporosis	5 (12.2)	4 (9.7)	1

AG, acromegaly group; CG, control group; n, number; m, meters; kg, kilograms; NA, not applicable; IGF-1, insulin like growth factor-1; kg/m2, kilograms per square meters.

According to the DRIs, both groups showed insufficient intake of fiber, omega-3, omega-6, vitamin A, vitamin E, and the minerals magnesium, potassium, and calcium.

In the AG group, the average intake of nutrients, BMD, and bone quality did not differ between patients with controlled disease compared with those with active acromegaly.

The AG group had a higher intake of carbohydrates, trans fats, omega-3, folic acid, thiamine, and the bioactive compound beta-carotene (all p <0.05 vs CG; Table 2). The CG showed a higher intake of the bioactive compound flavonol (p=0.008), while the intake of other nutrients, minerals, and bioactive compounds was similar between the groups (Table 2).

Table 2. Nutrient intake in the acromegaly (AG) and control group (CG)

Nutrients	**EAR**	**AG (n=41)**	**CG (n=41)**	***p***
Energy (kcal/day)		2242.3 ± 929.4	1958.4 ± 784.4	0.059
Macronutrients				
Proteins (g)	46-56	104.1 ± 45.1	104.1 ± 48.1	0.89
Men g/kg		1.17 ± 0.39	1.62 ± 0.80	0.042
Women g/kg		1.24 ± 0.60	1.37 ± 0.48	0.44
Carbohydrates (g)	130	267.8 ± 130.5	207.9 ± 96.5	**0.02**
Fibers (g)	25	19.2 ± 7.5	16.8 ± 7.6	0.08
Total fat (mg)	ND	71.9 ± 32.7	69.7 ± 33.5	0.64
Saturated (%/day)	< 10	25.6 ± 12.2	25.1 ± 10.5	0.83
Monounsaturated (g)	ND	23.6 ± 11.1	23.4 ± 12.2	0.73
Polyunsaturated (g)	ND	12.8 ± 5.9	12.3 ± 5.4	0.74
Cholesterol (mg)	<300	383.8 ± 179.8	426.8 ± 212.0	0.32
Trans fat (g)	<1%/day	2.9 ± 2.5	0.8 ± 0.6	<0.001
Omega-3 (g)	1.1-1.6	0.36 ± 0.24	0.21 ± 0.18	0.001
Omega-6 (g)	11-17	9.9 ± 5.0	9.1 ± 6.9	0.59

Micronutrients				
Vitamins				
B12 (mcg)	2.4	4.4 ± 2.3	4.8 ± 2.4	0.46
B6 (mg)	1.3-1.7	1.96 ± 0.97	1.83 ± 0.82	0.50
B9 (mcg)	400	460.4 ± 171.1	371.9 ± 172.0	0.01
B3 (mg)	14-16	25.2 ± 12.2	23.6 ± 11.9	0.53
B2 (mg)	1.1- 1.3	1.73 ± 0.68	1.65 ± 0.63	0.71
B1 (mg)	1.1- 1.2	1.58 ± 0.67	1.23 ± 0.51	0.009
A (mcg)	700- 900	174.1 ± 114.0	174.8 ± 96.1	0.97
C (mg)	75- 90	188.73 ± 136.7	145.5 ± 106.2	0.06
D (mcg)	5- 15	4.56 ± 4.63	4.55 ± 5.14	0.67
E (mg)	15	3.86 ± 2.32	4.56 ± 2.66	0.20
Minerals (mg)				
Iron	8- 18	10.4 ± 4.6	9.4 ± 3.7	0.23
Zinc	8- 11	12.8 ± 6.6	12.3 ± 5.4	0.80
Magnesium	310- 420	280.1 ± 90.5	259.9 ± 98.6	0.33
Potassium	4700	3056.6 ± 1144.7	2762.0 ± 0.964	0.27
Calcium	1000- 1200	636.1 ± 380.8	583.3 ± 281.7	0.93
Trace element				
Selenium (mcg)	55	101.9 ± 43.1	104.0 ± 44.5	0.82
Bioactive				
Compounds (mg)				
β-carotene (mcg)	ND	810.7 ± 592.2	252.6 ± 347.7	0.001
Flavone	ND	9.33 ± 5.27	5.27 ± 7.70	0.15
Flavonol	ND	16.0 ± 29.6	29.3 ± 30.2	0.008
Flavanone	ND	80.8 ± 76.1	50.6 ± 65.7	0.058

Isoflavone	ND	0.68 ± 0.71	0.66 ± 0.65	0.89
Anthocyanin	ND	27.4 ± 24.2	26.4 ± 21.1	0.83
Others				
Alcohol (g)	< 30	1.31 ± 3.7	9.10 ± 11.4	<0.001
Caffeine (mg)	400	84.5 ± 71.8	108.6 ± 107.0	0.323

RDA: Recommended Dietary Allowances; AG, acromegaly group; CG, control group; n, number; kcal, kilocalories; B12, methylcobalamin; B6, pyridoxine; B9, folic acid; B3, niacin; B2, riboflavin; B1, thiamine; *p, p value;* NA, not applicable; mcg, micrograms; mg, miligrams; g, grams; g/kg, grams per kilograms.

Compared to the CG, the AG had similar FRAX (major fracture risk: AG 1.6 ± 1.2 vs. CG 2.0 ± 1.5, p=0.68; hip fracture risk: AG 0.25 ± 0.43 vs. CG 0.45 ± 0.52, p=0.13) and similar BMD except for higher femoral neck BMD in men (0.043). They also had a higher number of total fractures per patient (0.63 ± 1.11 vs. 0.14 ± 0.43 in the AC and CG, respectively, p=0.001) and lower TBS (men AG 1.10 ± 0.43 vs. CG 1.43 ± 0.09; p=0.006; women AG 1.03 ± 0.54 vs. CG 1.35 ± 0.14; p=0,009), even corrected with TBS.

Table 3 - Bone Mineral Density (BMD), Trabecular Bone Score (TBS), Number of Fractures and FRAX in the acromegaly (AG) and control group (CG)

Parameter	AG (n=41)	CG (n=41)	P value
BMD (g/cm^2)			
Lumbar Spine			
Men	1.046 ± 0.145	1.033 ± 0.091	0.75
Women	0.945 ± 0.134	1.002 ± 0.220	0.29
Femoral Neck			
Men	0.950 ± 0.134	0.835 ± 0.178	0.04

Women	0.749 ± 0.100	0.773 ± 0.142	0.52
Total femur			
Men	1.049 ± 0.142	0.960 ± 0.119	0.05
Women	0.853 ± 0.109	0.828 ± 0.186	0.58
BMD (n, %)			
Low	21 (46.3)	20 (39.0)	0.82
Low bone mass	1 (2.4)	0 (0)	
Osteopenia	10 (24.4)	12 (29.3)	
Osteoporosis	8 (19.5)	4 (9.7)	
Fractures (n, %)			
History	8 (19.5)	2 (4.9)	0.88
VFA	10 (24.4)	3 (7.3)	0.06
Total fracture/patient	0.63 ± 1.11	0.15 ± 0.43	0.01
TBS			
Men	1.10 ± 0.43	1.43 ± 0.09	0.006
Women	1.03 ± 0.54	1.35 ± 0.14	0.009
Part. degraded (n, %)	10 (24.4)	11 (26.8)	0.015
Degraded (n,%)	11 (26.8)	3 (7.3)	
FRAX 2.0			
Major fracture (%)	1.6 ± 1.2	2.1 ± 1.5	0.28
Hip fracture (%)	0.25 ± 0.43	0.45 ± 0.52	0.13
FRAX with TBS 2.0			
Major fracture (%)	2.1 ± 1.6	2.0 ± 1.5	0.68
Hip fracture (%)	0.43 ± 0.72	0.48 ± 0.60	0.58

AG, acromegaly group; CG, control group; g/cm², grams per square centimeter; n, number; VFA, vertebral fracture assessment.

In the AG the intake of flavone and vitamin A were negatively correlated with total fractures. Several nutrients were positively associated with BMD in the AG, except for caffeine intake which showed a negative correlation with total hip BMD (p=0.011) (Table 4). The same was observed with TBS which was positively correlated with flavone, anthocyanin, beta-carotene, and vitamin C, and negatively correlated with saturated fats (p=0.035).

Table 4. Correlation between bone mineral density and TBS with nutrient intake.

Nutrients	BMD			TBS	TOTAL FRACTURES
	Spine	Femoral Neck	Total Hip		
Bioactive compounds					
Flavonol	ρ=0.315 p=0.048	-	-	-	-
Flavone	-	-	-	ρ=0.350, p=0.042	R= -0.338, p=0.031
Isoflavone	ρ= 0.390, p=0.013	-	-	-	-
Flavonone	-	-	-	ρ= 0.557, p=0.001	-
Anthocyanin	ρ= 0.320, p=0.044	-	-	ρ= 0.392, p=0.022	-
Beta-carotene	-	-	-	R= 0.356, p=0.039	-
Macronutrients					
Proteins	-	ρ= 0.326, p=0.040	-	-	-
Total lipids	-	ρ= 0.393, p=0.012	ρ= 0.411, p=0.08	-	-
Saturated fats	-	-			-
Omega 3	-	-	-	-	-
Omega 6	-	R= 0.359, p=0.023	R= 0.332, p=0.036	-	-
MUFA	-	ρ= 0.492, p=0.001	ρ= 0.500, p=0.001	-	-
PUFA	-	R= 0.365, p=0.021	-	-	
Minerals					
Iron	-	ρ= 0.322, p=0.043	-	-	-
Zinc	-	ρ= 0.320, p=0.044	ρ= 0.326, p=0.04	-	-
Selenium	-	R= 0.330, p=0.033	R= 0.360, p=0.022	-	-
Vitamins	-	-	-	-	-
Niacin	-	-	-	-	-
Vitamin A	-	-	-	-	R= -0.321, p=0.041
Vitamin C	-	-	-	ρ= 0.447, p=0.008	-
Vitamin E		R=0.330, p=0.037			
Others	-	-	-	-	-
Caffeine	-	-	ρ= -0.354, p=0.025	-	-

Abbreviations: BMD= bone mineral density; TBS= trabecular bone score; R= Pearson's correlation; ρ= Spearman's correlation;

DISCUSSION

Understanding the impact of nutrient intake on bone mineral density (BMD) and bone quality in patients with acromegaly is crucial for the proper management of this condition. To our knowledge, this is the first study to evaluate nutritional intake in patients with acromegaly and its association with bone characteristics and the prevalence of fractures. We have demonstrated that patients with acromegaly had adequate bone mass, but poorer bone quality and a higher number of fractures associated with anti-inflammatory and antioxidant nutrients.

Bone density and quality

We have demonstrated that patients with acromegaly had adequate bone mass, but poorer bone quality and a higher number of fractures, which is aligned with a metanalysis with 1.935 patients with acromegaly, which did not show significant differences in BMD, but a high prevalence of vertebral fractures, related to disease activity (6). In our cohort, 24% of patients with acromegaly presented with fractures, while up to 80% of vertebral fractures have been reported in some studies with long follow-up periods, even in patients with controlled disease (31) (32).

The TBS of participants with acromegaly indicated degraded trabecular microarchitecture, which was consistent with other studies and may explain the fractures. The impaired bone microarchitecture may result from an imbalance between bone formation and resorption, influenced by excess GH and IGF-1(33) (34)

Nutrient intake

Daily intake of magnesium, calcium, and vitamin D, which are important nutrients for bone health, was below the recommended for age and sex in the AG,

but this finding was also observed in the CG, suggesting that this was not an essential factor to explain the bone abnormalities observed in patients with acromegaly. Accordingly, alcohol consumption, which could increase the risk of falls and consequently fractures, was higher in the CG and could be also eliminated as a risk factor (35).

According to the WHO, saturated fat intake should be below 10% of total daily energy intake. The mean intake of fat was 25g/day in both groups. Given a standard 2,000 kcal diet, this amount corresponds to 225 kcal from fat, indicating that both groups exceeded the recommended intake. Moreover, many participants consumed less than 2000 kcal, so their saturated fat intake exceeded 10%. Notably, patients with acromegaly had a higher intake of trans fat, which is produced through the partial hydrogenation of vegetable oils and is associated with a 34% increase in all-cause mortality risk and is linked to inflammatory and oxidative stress (36).

High carbohydrate intake has been associated with poor bone health (8). Currently, the WHO's recommendation for carbohydrate intake is ≥400g per day for individuals over 10 years, mainly derived from fruits and vegetables (28). Participants with acromegaly had a higher intake of carbohydrates compared to the CG, an average of 267g derived from pasta, cookies, biscuits, and bread, highlighting the lower-than-recommended intake of fruits and vegetables.

A pattern of positive correlations was observed in our study between bone mass and quality parameters with nutrients with antioxidant and anti-inflammatory properties. Among the bioactive compounds, beta-carotene and the flavonoid group — the most abundant dietary polyphenols, with subclasses such as anthocyanins, flavanols, flavanones, and isoflavones — showed positive correlations with BMD. Studies evaluating these compounds found similar beneficial effects from their consumption or supplementation on bone mass, with increased BMD (37) (38), (39),

reduced risk of osteoporotic fractures (40), and reduced bone degradation (15). These nutrients may contribute to bone protection by reducing the harmful effects of free radicals and interleukins, known to negatively impact bone metabolism.

Additionally, monounsaturated and polyunsaturated fatty acids, such as omega-3, were also associated with better BMD, as shown in another study (41). Among the minerals, zinc showed a positive correlation with bone density, potentially supporting an increase in BMD. Zinc demonstrates a pronounced effect on bone health (42, 43), helping reduce interleukins and reactive oxygen species, which are harmful to bone tissue (44).

Despite the higher intake of nutrients beneficial to overall health and with potential impact on bone mass, this intake did not seem to overcome the effects of the disease on BMD and bone quality in patients with acromegaly. Future studies should explore the impact of specific diets and nutritional supplements on bone health in patients with acromegaly to identify interventions that may mitigate the disease's negative effects.

Limitations and Strengths

The limited number of participants, the heterogeneity of the acromegaly group, and the cross-sectional nature of the analysis limit the generalization of the findings and the ability to establish causal relationships. Additionally, the influence of dietary supplements and medications on BMD was not evaluated, which may have impacted the observed results. The strength of this study was the novelty of studying the dietary components of patients with acromegaly and their potential relation with skeletal quality and fractures, which are well-known complications of the disease.

CONCLUSION

In conclusion, we have observed that individuals with acromegaly had low bone quality and a higher prevalence of fractures, despite adequate bone mass as evaluated by DXA. Inadequate intake of compounds with antioxidant and anti-inflammatory properties, combined with excessive consumption of trans fats and poor-quality carbohydrates, may be additional factors contributing to these findings.

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The Relationships Among Nutrition, Body Composition, Muscle Strength and Physical Performance in Patients with Acromegaly

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ABSTRACT

Aim: Acromegaly is a chronic, insidious disorder characterized by excessive secretion of growth hormone (GH), which stimulates hepatic secretion of insulin-like growth factor 1 (IGF-1). These hormonal alterations can impact body composition, strength, and physical performance in affected individuals. The quality of nutrient intake may modulate the effects of this hormonal excess. The aim of this study was to investigate the impact of dietary profile on body composition, physical performance, and muscle strength in patients with acromegaly. **Methods:** Observational, cross-sectional study involving patients with acromegaly receiving care at a tertiary center, compared with age- and sex-matched controls. Body composition including [total lean mass (TLM) and appendicular lean mass (ALM)] was assessed using dual-energy X-ray absorptiometry (DXA). All participants completed a Food Frequency Questionnaire (FFQ) and underwent strength and performance testing. **Results:** A total of 82 patients were included, 41 in the acromegaly group (AG) and 41 in the control group (CG). The AG comprised 23 women (56.1%) and 18 men (43.9%), mean age of 58.3 years and mean BMI of 31.1 ± 5.2 kg/m². The AG exhibited a higher intake of carbohydrates, trans fats, and certain micronutrients, including omega-3, vitamin B9, and beta-carotene, compared to the CG. Nutrients like niacin (R=-0.316, p=0.004) and vitamin B6 (R=-0.320, p=0.042) were found to influence performance on the sitt to stand test. Beta-carotene (R=-0.429, p=0.005), vitamin E (R=-0.321, p=0.041), and flavone (R=-0.313, p=0.046) were positively associated with better time to get up and go (TUG) test, whereas caffeine intake (R=0.344, p=0.028) was negatively associated. Additionally, niacin (R=0.341, p=0.029) and selenium (R=0.317, p=0.046) had a positive impact on the short physical performance battery (SPPB) test. Hand grip strength was positively correlated with monounsaturated fats (R=0.387, p=0.012) and selenium (R=0.316, p=0.044). Several nutrients, including selenium, zinc, omega-6 fatty acids, calcium, and iron, were positively associated with TLM, while caffeine and isoflavones were linked to a negative impact. **Conclusion:** Patients with acromegaly often exhibit increased muscle mass; however, their functional capacity may be compromised, potentially due to alterations in muscle

composition. The intake of nutrients such as selenium, β-carotene, flavonoids, vitamin E, and niacin may improve physical performance and muscle strength.

Keywords: Acromegaly; Nutrients intake; Body composition; Physical performance; Muscle mass.

INTRODUCTION

Acromegaly is a rare endocrine disorder characterized by excessive secretion of growth hormone (GH) and insulin-like growth factor 1 (IGF-1), typically due to a GH-secreting pituitary adenoma. This hormonal excess leads to a range of clinical features and comorbidities (1), which induces significant body changes and increases the risk of comorbidities, accompanied by notable alterations in body composition. Patients with active disease often exhibit a reduction in visceral fat mass and an increase in skeletal muscle mass and extracellular body water (1). Although increased muscle mass may suggest an improved physical ability, elevated growth hormone (GH) and insulin-like growth factor I (IGF-I) levels can negatively impact peripheral muscle strength, exacerbating musculoskeletal weakness (2).

Muscle health maintenance relies on essential nutrients. Proteins and amino acids play a central role in preserving and increasing muscle mass by stimulating muscle protein synthesis. Studies indicate that adequate protein intake combined with resistance training are crucial for promoting muscle anabolism (3). Furthermore, higher intake of proteins and dietary fiber has been associated with lower body fat percentage and body mass index (BMI), demonstrating benefits for body composition and fat control (4). Polyunsaturated fatty acids, such as omega-3, known for their anti-inflammatory properties, also contribute to increased muscle mass and strength by modulating anabolic signaling pathways. These lipids are further associated with reduced central adiposity, particularly when combined with strength training (5).

Antioxidant vitamins (C and E) play a crucial role in protecting muscle tissue from oxidative stress, thereby supporting muscle health (6)(7). In addition, other nutrients such as iron, niacin, zinc, vitamin B12, selenium, and proteins are beneficial to lean mass (8). Specifically, zinc plays a critical role in protein synthesis and maintenance of lean mass, and its deficiency has been linked to increased fat deposition (9). While some nutrients demonstrate beneficial effects on body composition and muscle strength, others may exert negative impacts. Trans fats, for instance, are associated with detrimental effects on skeletal muscle mass (10). These lipids impair insulin sensitivity in muscle, interfering with energy metabolism and potentially contributing to a progressive decline in muscle strength and function (11)(12). This effect may exacerbate insulin resistance, to which individuals with acromegaly are more susceptible due to the excess of GH and IGF-1 (13).

Chronic alcohol consumption is also linked to a reduction in muscle mass and strength, largely attributed to the inhibition of protein synthesis and the increased rate of muscle degradation (14)(15).

Given the limited literature on the nutritional intake of patients with acromegaly and its effects on body composition, physical performance, and muscle strength, this study aims to evaluate the influence of diet quality on these parameters.

SUBJECTS AND METHODS

This was an observational, cross-sectional study which evaluated patients with acromegaly followed at the Neuroendocrine Unit of the Endocrine Division (SEMPR) in a university hospital. The study was approved by the Ethics Committee of our institution under the protocol number 6.293.233 (CAAE: 49629321.7.0000.0096), and all individuals who agreed to participate signed an informed consent form.

Patients with acromegaly of both sexes over the age of 18 were invited to participate out of convenience during their routine outpatient medical appointment. The exclusion criteria included uncontrolled metabolic or chronic diseases or active malignant neoplasms; use of medications or drugs that could affect muscle or bone, those with any physical impairment preventing functional physical analysis and patients that were unable to perform the required tests and exams.

The included patients with acromegaly comprised the acromegaly group (AG) and completed a standardized questionnaire about demographic data, disease characteristics, type of treatment, medications in use, physical activity, lifestyle habits (smoking and alcohol consumption), personal and family history of fractures, and the presence of comorbidities. Data not captured during the interview was collected from medical records. The participants were then referred for nutritional and physical evaluations (weight, height, and body mass index [BMI]), body composition assessment, strength and functional tests.

The diagnosis of acromegaly was based on the 14th Acromegaly Consensus, and the AG was considered to have controlled disease if the IGF-1 levels were within the normal reference range for age and sex (16). A control group (CG), matched by sex and age, was recruited from relatives of patients and individuals from the community.

Body Composition

Body composition was assessed using dual-energy X-ray absorptiometry (DXA) with a Hologic Horizon A device – serial number 201383, Bedford, USA. Parameters analyzed included total lean mass in grams (TLM), percentage of total fat mass (%TFM), android/gynoid ratio (A/G), and appendicular lean mass (ALM), measured by the sum of lean mass in the arms and legs. Weight was measured using a calibrated anthropometric scale (Plenna®) with the participant barefoot. Height was measured using a vertical stadiometer (Tonelli Gomes®). Body mass index (BMI) was calculated by dividing weight (in kg) by height squared (in meters). BMI results for participants were classified as underweight (BMI < 18.5 kg/m²), normal weight (18.6 kg/m² < BMI < 24.9 kg/m²), overweight (25.0 kg/m² < BMI < 29.9 kg/m²), obesity grade I (30.0 kg/m² < BMI < 34.9 kg/m²), obesity grade II (35 kg/m² < BMI < 39.9 kg/m²), and grade III obesity (BMI > 40 kg/m²) (17).

Physical Performance and Muscle Strength

Physical performance and strength were evaluated using the short physical performance battery (SPPB), which comprises three tests: strength, performance, and balance. Strength was assessed through the 5-times seat to stand test (STST), where patients were required to rise from and sit back on a chair five consecutive times as quickly as possible without stopping or using their arms. A time below 15 seconds (s) was considered normal. Performance was measured using the 4-meter gait speed test (GS), in which patients stood up from a chair, walked 6 meters at a safe speed, the first and last meters were not counted; a speed of less than 0.8 m/s was acceptable (18). Balance was evaluated by instructing patients to maintain a standing position without support for 10 s with their feet together, followed by another 10 s in a semi-tandem position, and then 10 s in a tandem position. Each position was scored: maintaining the position for 10 s earned 2 points, holding it for 3 to 9.99 s earned 1 point, and less than 3 s or inability to perform resulted in 0 points (18). Additionally, the time up and go test (TUG) was conducted, requiring patients to stand from a chair without using their arms, walk 3 meters, turn around a cone, return, and sit back down at a comfortable pace. A time of 20 s or less was considered normal (18)(19). Upper limb strength was assessed using the handgrip strength (HGS) test with a Charder® MG 4800 dynamometer. Patients were instructed to squeeze the dynamometer handle with maximum strength, and an

average of three attempts was recorded. Values of ≤27 kg for men and ≤16 kg for women were considered altered (18)

Food Frequency Questionnaire (FFQ)

To assess dietary patterns and nutrient intake, a validated food frequency questionnaire (FFQ) was used for the adult Brazilian population aged 18 to 60 years, who were overweight, i.e., BMI above 25 kg/m² (20). The FFQ was collected considering the foods consumed over a one-month period and includes 90 foods or preparations, divided into fifteen sections: 1) foods or preparations; 2) pasta; 3) various dishes and snacks; 4) meats; 5) rice, tubers, and vegetables; 6) eggs; 7) dairy products; 8) fats; 9) cereals; 10) green leaves; 11) fruits and juices; 12) miscellaneous; 13) breads, cakes, and cookies; 14) various drinks; and 15) sweets and desserts. During the interview, the participant was asked to indicate whether they consumed the food or preparation, the frequency throughout the month, and the amount consumed in household measures or the approximate value in grams.

To assist in reporting quantities, photos of household measuring utensils and dishes were shown to observe and define the proportion of the plate occupied by the food, to estimate as closely as possible the amount consumed (21). FFQ data were entered into a pre-designed Excel® spreadsheet, which displayed the quantities of 38 macronutrients, micronutrients, and bioactive compounds per 100 grams of food or preparation. A formula was created, so when the quantity consumed by the patient was entered into the spreadsheet, the calculation would be automatic. The calculation of dietary component intake used the Brazilian food composition table (TACO) (22), the USDA food and nutrient database (23), the Brazilian table of carotenoid composition in foods (24), and the Phenol-Explorer 3.0 database (25). The reference values for nutrient intake were derived from the International Life Science Institute of Brazil (ILSI) publication titled *"Nutrient Recommendations"* and were based on the Estimated Average Requirement (EAR). The EAR represents the daily intake level of a nutrient estimated to meet the requirements of 50% of healthy individuals within a specific age and sex group. This value corresponds to the median of the nutrient requirement distribution and aligns with the mean when the distribution is symmetric (26), and the latest WHO guidelines on fat and carbohydrate consumption (27)(28).

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 29. A descriptive analysis of the frequency distribution of all variables was conducted. The Kolmogorov-Smirnov test was used to assess the normality of the variables in the study. To evaluate differences between means, Student's t-test was used for parametric data and the Mann-Whitney test for non-parametric data. For the evaluation of categorical data, Fisher's exact test and the chi-square test were used. We utilized the Spearman's Rho coefficient to measure the size of the effect of the studied associations, assuming the following cutoff points: at least 0.8 (very strong), 0.6 up to 0.8 (moderately strong), 0.3–0.5 (fair), and <0.3 (poor) (29). Statistical significances were considered when the p-value was ≤ 0.05.

RESULTS

Fifty-seven patients with acromegaly were invited to participate, 8 were excluded either because they lived outside town and could not do the evaluations or had a condition that could impact the test results. Additionally, eight individuals declined to answer the FFQ. Finally, 41 patients were included in the AG (mean age 55.9 ± 11.8 years; 90.2% white and 58.5% women; BMI 31.3 ± 5.2 kg/m²) and were compared to 41 in the CG (mean age 56.8 ± 14.3 years; 82.9% white and 56.1% women; 25.5 ± 3.3 kg/m²). The mean age at diagnosis of acromegaly was 43.7 ± 13.0 years, the diagnosis occurred in an average of 12 years earlier. Most of the AG underwent surgical treatment.

Compared to the CG, the AG group had higher BMI, more fractures, and higher number of comorbidities, with hypertension, obesity, and hypogonadism being the most prevalent (p<0.05 for all) (Table 1).

Table 1. Clinical characteristics of the study groups

Characteristics	Acromegaly Group (n=41)	Control Group (n=41)	*p*
Age, (years)	55.9 ± 11.8	56.8 ± 14.3	0.769[1]
Ethnicity			0.010
White, n (%)	38 (92.7)	34 (82.9)	
Black, n (%)	3 (7.3)	1 (2.4)	
Asian, n (%)	0	6 (14.6)	

Sex, n (%)			
Women	23 (56.1)	23 (56.1)	
Men	18 (43.9)	18 (43.9)	
Smoking, n (%)	7 (17.1)	1 (2.4)	0.020
Height (m)	1.7 ± 0.1	1.64 ± 0.1	0.445[1]
Weight (Kg)	87.0 ± 18.6	70.1 ± 11.3	<0.001[1]
BMI (kg/m²)	31.1 ± 5.2	25.5 ± 3.3	<0.001[2]
Normal, n (%)	6 (14.6)	25 (61.0)	
Overweight, n (%)	15 (36.6)	11 (26.8)	
Obesity grade I, n (%)	10 (24.4)	5 (12.2)	
Obesity grade II, n (%)	7 (17.1)	0	
Obesity grade III, n (%)	3 (7.3)	0	
Disease data			
Time since diagnosis (years)	12.0 ± 7.8	NA	
Age at diagnosis (years)	43.7 ± 13.0	NA	
Serum IGF-1*, ng/ml	256.6 ± 164.8	NA	
Surgical treatment, n (%)	35 (85.4%)	NA	
Medications, n (%)			
Somatostatin receptor ligands			
Octreotide	26 (63.4)	NA	
Lanreotide	15 (36.6)	NA	
Cabergoline	7 (17.1)	NA	
Pegvisomant	4 (9.7)	NA	
Comorbidities, n (%)			
Hypertension	23 (56.1)	14 (34.1)	0.057
Obesity	20 (48.8)	6 (14.6)	0.001
Dyslipidemia	16 (39.0)	12 (29.3)	0.390
Diabetes	15 (36.6)	3 (7.3)	0.003
Hypothyroidism	9 (21.9)	1 (2.4)	0.010
Hypogonadism	9 (21.95)	0	<0.001
Men	4 (44.4)	0	
Hormonal replacement	1 (25.0)	0	
Women	5 (55.5)	0	
Hormonal replacement	4 (80.0)	0	
Hypopituitarism	7 (17.1)	0	0.010
Mood disorder	6 (14.6)	0	0.032
Osteoporosis	5 (12.2)	4 (9.7)	1.000

Abbreviations: NA, not applicable; BMI, body mass index; kg/m^2, kilograms per square meters; *, value of IGF at the time of evaluation; n, number; g, grams; kg, kilograms; ng/ml, nanograms per milliliter; IGF-1, insulin like growth factor-1.

Despite variations in the intake of certain nutrients and bioactive compounds, nutritional deficiencies were common in both groups (Table 3). The AG had higher intake of carbohydrates ($p = 0.023$), trans fats ($p < 0.001$), omega-3 ($p = 0.002$), folic

acid (p = 0.022), thiamine (p = 0.009), beta-carotene (p < 0.001) and flavanol (p<0.001). The mean mineral intake was similar between the groups. Both groups showed insufficient daily consumption of fiber, omega-3, omega-6, vitamins A, E, magnesium, potassium, and calcium and only the CG had an intake below the recommended of folic acid.

Table 2. Nutrient intake in the study groups

Nutrients	RDA	AG (n=41) Average ± SD	CG (n=41) Average ± SD	*p*
Energy (kcal)		2242.34 ± 929.36	1958.42 ± 784.35	0.059[2]
Macronutrients				
Proteins (g)	46 to 56	104.147 ± 45.13	104.13 ± 48.12	0.893[2]
Carbohydrates (g)	100	267.78 ± 130.47	207.88 ± 96.50	0.019[2]
Fibers (g)	25 to 38	19.20 ± 7.50	16.78 ± 7.63	0.084[2]
Total fat (g)	ND	71.86 ± 32.73	69.69 ± 33.47	0.640[1]
Saturated (g)	<10% / day	25.58 ± 12.16	25.13 ± 10.53	0.835[2]
Monounsaturated (g)	ND	23.59 ± 11.12	23.38 ± 12.16	0.738[2]
Poliunsaturated (g)	ND	12.82 ± 5.86	12.26 ± 5.36	0.745[1]
Cholesterol (mg)	<300	383.79 ± 179.79	426.79 ± 212.00	0.325[1]
Trans fat (g)	<1% / day	2.86 ± 2.55	0.76 ± 0.60	<0.001
Omega-3 (g)	1.1 - 1.6	0.36 ± 0.24	0.21 ± 0.18	0.001[2]
Omega-6 (g)	11 - 17	9.86 ± 5.02	9.15 ± 6.87	0.594[1]
Micronutrients				
Vitamins				
Vitamin A - mcg	500 - 625	174.07 ± 113.96	174.82 ± 96.15	0.974[2]
Vitamin C - mg	60 - 75	188. 73 ± 136.66	145.48 ± 106.18	0.068[2]
Vitamin D – mcg	10	4.56 ± 4,63	4.55 ± 5.14	0.670[2]
Vitamin E - mg	12	3.86 ± 2.32	4.56 ± 2.66	0.208[2]
B12 - mcg	2.0	4.44 ± 2.26	4.76 ± 2.42	0.467[2]
B6 - mg	1.1 - 1.3	1.96 ± 0.97	1.83 ± 0.82	0.503[1]
B9 - mcg	320	460.42 ± 171.09	371.86 ± 171.96	0.013[2]
B1 - mg	0.9 - 1.0	1.58 ± 0.67	1.23 ± 0.51	0.009[2]
Minerals				
Calcium (mg)	800 - 1000	636.08 ± 380.79	583.27 ± 281.71	0.935[2]
Magnesium (mg)	255- 350	280.13 ± 90.54	259.91 ± 98.59	0.336[1]
Potassium (mg)	2600 to 3400	3056.63 ± 1144.71	2762.02 ± 0.964	0.272[2]
Zinc (mg)	6.8 – 9.4	12.79 ± 6.57	12.26 ± 5.36	0.802[2]
Trace element				
Selenium (mcg)	45	101.91 ± 43.08	104.02 ± 44.48	0.828[1]

Bioactive compounds				
Betacarotene (mcg)	ND	810.71 ± 592.22	252.65 ± 347.75	0.001[1]
Flavone (mg)	ND	9.33 ± 5.27	5.27 ± 7.70	0.153[2]
Isoflavone (mg)	ND	0.68 ± 0.71	0.66 ± 0.65	0.893[2]
Others				
Alcohol (g)	<30	1.31 ± 3.66	9.10 ± 11.43	<0.001
Caffeine (g)	400	84.48 ± 71.85	108.63 ± 107.04	0.323

Abbreviations: RDA: Recommended Dietary Allowances; AG, acromegaly group; CG, control group; n, number; kcal, kilocalories; B12, methylcobalamin; B6, pyridoxine; B9, folic acid; B1, thiamine; *p, p value;* ND, not defined; mcg, micrograms; mg, miligrams; g, grams; g/kg, grams per kilograms.

The body composition showed a similar %TFM, as well as a comparable A/G. However, the two parameters of lean mass were higher in the AG, as follows: TLM (male AG 66.7 ± 8.9 Kg vs CG 52.3 ± 8.6 kg, p<0.001 and female AG 47.1 ± 9.1 kg vs CG 38.7 ± 6.0 kg, p=0.001) and ALM (male AG 27.7 ± 4.3 kg vs CG 22.3 ± 3.1 kg, p<0.001 and female AG 16.9 ± 6.4 Kg vs CG 15.0 ± 2.4 Kg, p=0.009).

Table 3. Body Composition in the study groups.

	Acromegaly Group (n=41)	Control Group (n=41)	p
Total lean mass (kg)			
Men	66.7 ± 8.9	52.3 ± 8.6	<0.001
Women	47.1 ± 9.1	38.7 ± 6.0	0.001
Total fat mass (%)			
Men	32.0 ± 3.5	31.2 ± 4.0	0.528
Women	41.3 ± 5.6	42.0 ± 3.7	0.644
ALM (kg)			
Men	27.7 ± 4.3	22.3 ± 3.1	<0.001
Women	16.9 ± 6.4	15.0 ± 2.4	0.009
A/G ratio			
Men	1.11 ± 0.17	1.07 ± 0.14	0.445
Women	0.89 ± 0.11	0.91 ± 0.12	0.543
Elevated A/G ratio, n (%)			
Men	14 (87.5)	17 (89.5)	0.855
Women	13 (59.09)	13 (68.4)	0.536

Abbreviations: ALM, appendicular lean mass; kg, kilogram; w, weight; A/G, android/gynoid ratio; n, number.

Detailed data on physical performance and muscle strength are presented in Table 4. Compared to CG, the AG was slower in STST (16.6 s ± 5.3 s vs 12.2s ±

2.5s; p<0.001), in the TUG (12.22 s ± 4.27 s vs 9.4 s ± 2.7 s; p<0.001) and GS (0.91 m/s ± 0.3 m/s vs 1.16 m/s ± 0.2 m/s; p<0.001), and performed worst in the SPPB (9.0 ± 2.6 vs CG 11.8 ± 0.5; p<0.001).

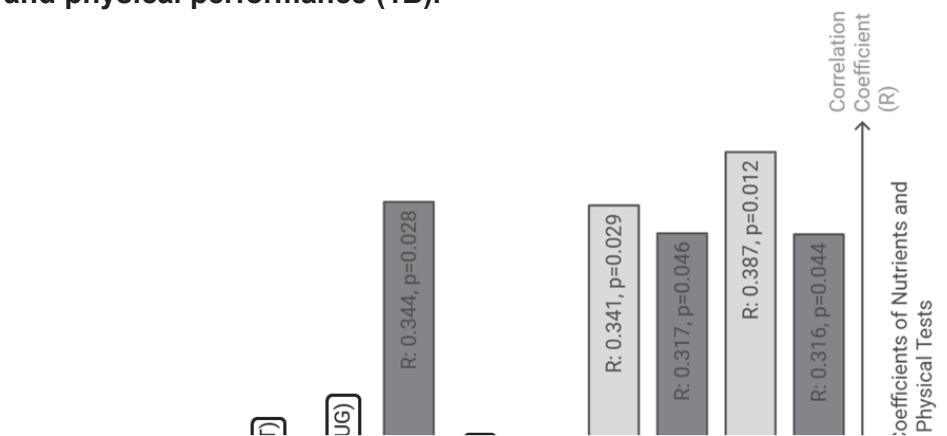
Table 4. Physical performance and muscle strength in the study groups

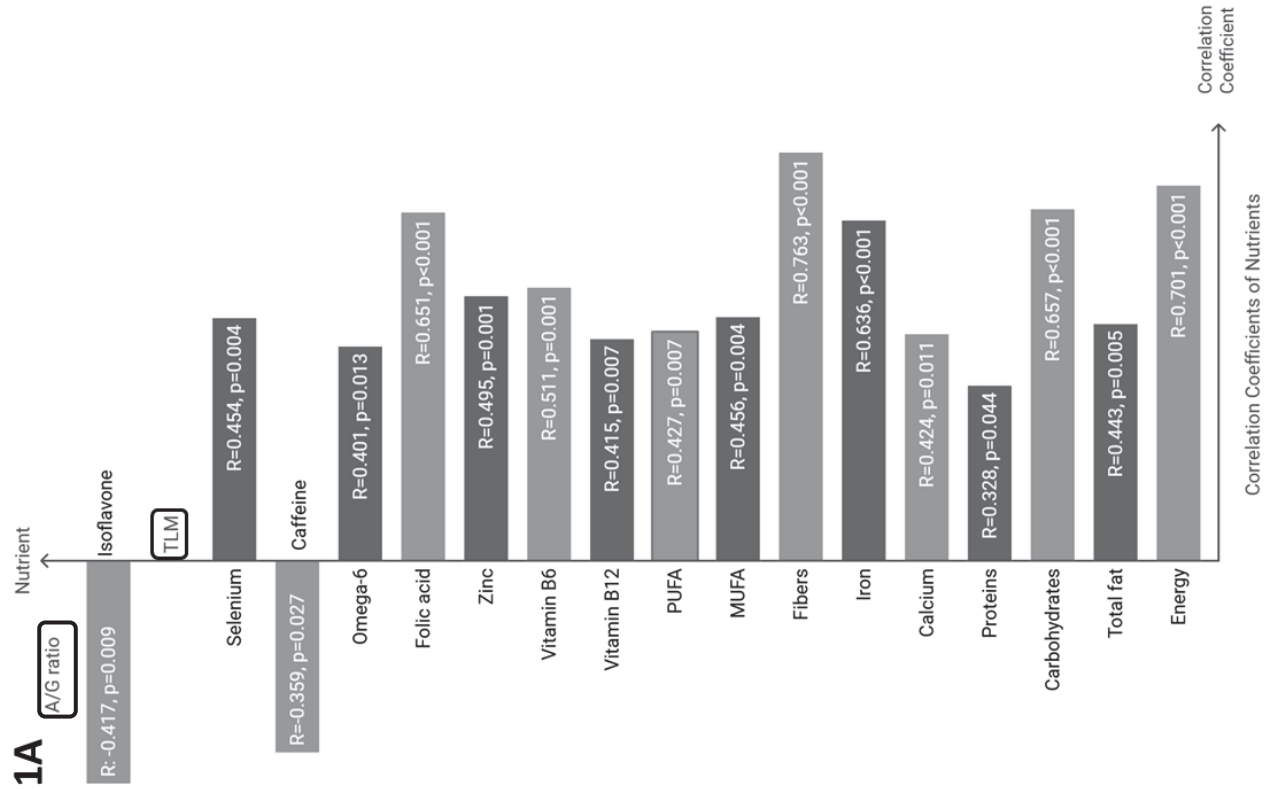
Tests	Acromegaly Group (n=41)	Control Group (n=41)	*p*
Muscle Strength			
STST (s)	16.6 ± 5.3	12.2 ± 2.5	<0.001
Low n (%)	22 (53.6)	2 (4.9)	<0.001
HGS (kg)			
Men	42.1 ± 9.3 (0)	39.4 ± 5.8 (0)	0.293
Low, n (%)	0 (0)	0 (0)	
Women	25.7 ± 5.8 (1)	24.6 ± 4.7 (0)	0.488
Low, n (%)	1 (2.43)	0 (0)	1.000
Physical performance			
TUG (s)	12.22 ± 4.27	9.4 ± 2.7	0.001
Altered, n (%)	3 (7.3)	1 (2.4)	0.616
GS (m/s)	0.91 ± 0.3	1.16 ± 0.2	<0.001
Altered, n (%)	12 (29.3)	3 (7.3)	0.020
SPPB	9.0 ± 2.6	11.8 ± 0.5	<0.001
Altered	13 (31.7)	0 (0)	<0.001

Abbreviations: n, number; %, percentage; s, seconds; kg, kilograms; m/s, meters per second; SPPB, short physical performance battery.

Correlations between body composition, physical performance tests, muscle strength and the intake of nutrients and bioactive compounds in the AG are detailed in Figure 1. The A/G correlated negatively only with isoflavone, while TLM correlated positively with several nutrients, as selenium, omega-6, folic acid, zinc, vitamins B6 and B12, PUFA, MUFA, iron, fiber, calcium, proteins, carbohydrates, total fat, and total calories (p<0.05 for all). Only caffeine showed a negative correlation with TLM (Figure-1A). The performance of the TUG test was better with higher intake of the bioactive compounds beta-carotene, flavonoids, and vitamin E, which showed an inverse correlation with the time to execute the test, while caffeine showed a positive correlation and increased the time of the test. Strength was better with the intake of monounsaturated fats, selenium, niacin and vitamin B6 which correlated positively with HGS and negatively with STST, respectively. Niacin and selenium intake correlated positively with the SPPB, while no correlations were found between nutrients with the GS (Figure-1B).

Figure 1- Correlation between nutrients and body composition (1A), muscle strength and physical performance (1B).





Abbreviations: PUFA: Polyunsaturated fats; MUFA: monounsaturated fats; TLM: total lean mass; A/G: android/gynoid ratio; TUG: time up and go test; STST: sit-to-stand test; HGS: handgrip strength; SPPB: Short Physical Performance Battery; R: Spearman's rho; p= p value.

Although higher ALM and TLM were seen in patients with uncontrolled disease (ALM - 25.16 ± 5.6 kg uncontrolled vs. 19.25 ± 8.0 kg controlled, p=0.028 and TLM - 61.5 ± 12.5 kg uncontrolled vs. 51.3 ± 12.5 kg controlled, p=0.019) no correlation was found between disease activity and nutrients intake.

Nutrient intake had no impact when comparing patients with controlled versus uncontrolled acromegaly.

DISCUSSION

This is the first study, to our knowledge, to evaluate dietary quality in patients with acromegaly and associate it with body composition, physical performance and muscle strength. Nutritional intakes were different between patients and controls with deficiencies in diverse nutrients and bioactive compounds in both groups. There was a discrepancy in the AG between the higher TLM with worst strength and performance, which was associated with modifications in the diet quality.

Patients with acromegaly presented significantly higher total body weight compared to the CG as expenses of lean mass. The higher TLM in the AG could be attributed to the anabolic role of GH and IGF-1 in promoting protein synthesis. Previous studies support the altered body composition in acromegaly, characterized by increased skeletal muscle mass and reduced body fat (30)(31). However, in our sample, there was no significant difference in body fat percentage or A/G between groups, suggesting that the weight gain in patients with acromegaly was predominantly due to increased lean mass, which may also reflect an increase in intramuscular water. This increase in TLM was also associated with the intake of various nutrients, such as vitamins (B6, B9, and B12), minerals like iron, zinc, calcium, and selenium, as well as macronutrients including carbohydrates, proteins, and total fats, reinforcing the role of diet in modulating this variable.

It was observed that, despite having greater lean mass, patients with acromegaly exhibited a functional deficit, indicating muscle weakness, as previously reported (32). This deficit was evident in the results of physical performance tests, where individuals with acromegaly performed worse compared to CG. This altered functionality may be related to increased collagen deposition in muscle tissues, impairing flexibility, and muscle efficiency (33). A study by Martel-Duguech et al. found that patients with acromegaly had slower gait speed and poorer performance in the sit-to-stand test (32), corroborating the findings of our study. Several nutrients have been positively correlated with better physical performance and body composition. A balanced and nutrient-rich diet contributes to better performance when compared to a nutritionally poor diet (34)(35). The positive association between vitamin B6 intake and improved performance has been previously demonstrated (36). However, lower intakes of carbohydrates, omega-3, vitamin D, and saturated fats have been previously observed in individuals with greater frailty (37). Although in our study, the AG had higher carbohydrate and omega-3 intakes compared to the CG,

this finding did not translate into better muscle strength and performance. Saturated fat intake, despite being similar between groups, exceeded the recommendations in both groups. In a study involving women, aged 18-79 years, saturated fat intake was inversely associated with lean mass (10), whereas in a study with sedentary men aged 25-45 years, a high-fat diet was associated with reduced body efficiency (38). Despite this, the mean HGS was similar between the groups, but better when selenium and MUFA intake were higher. A study using data from the National Health and Nutrition Examination Survey (NHANES 2011-2014) observed that higher serum selenium concentrations were associated with better HGS (39). TLM was positively influenced by several nutrients, including minerals, vitamins, carbohydrates (including fiber), and fat. Hence, these results suggest that a higher intake of these elements might enhance lean mass in these individuals. In the study conducted by Borda et al. (8) with older adults, positive correlations were identified between ALM and the intake of PUFAs, zinc, selenium, vitamin B12, niacin, vitamin D, iron, and proteins. These findings highlight the significant role of these nutrients in supporting increased lean mass (8). In our study, the daily intake of fiber, omega-3, vitamins A, D, and E, magnesium, and calcium, although below the recommended levels for age and sex, showed a positive correlation with body composition and muscle strength. However, since there was no significant difference in the mean intake of these nutrients between the AG and the CG, it is possible to hypothesize that the performance in the AG could have been superior if these nutrients were consumed in the minimum recommended daily amounts, potentially offsetting the negative effects caused by the disease. Alcohol consumption, which is known to negatively impact muscle mass (14)(15) was higher in the CG, raising the possibility that it may not represent a significant risk factor in this context, or the increased alcohol intake in the CG may have impacted a lower lean mass compared to the AG.

Carbohydrates are the primary energetic source for exercise, especially high-intensity activities, having an important impact on physical performance and muscle strength. Muscle glycogen is the storage form of carbohydrates and in low quantities interferes with physical performance (40). We observed a higher intake of carbohydrates in the AG, which is likely due to the higher basal metabolism and total energy expenditure in patients with the disease (41)(42). Surprisingly, the high consumption of carbohydrates in our patients with acromegaly was not associated with better physical performance, suggesting that other variables are more important

in the physical performance and are not compensated by higher carbohydrate intake. The folic acid (vitamin B9), essential for red blood cell production, DNA synthesis, and amino acids (33), was not effective in improving physical function and performance in a two-year study of elderly individuals supplemented simultaneously with vitamin B12, which is in agreement with our data, that despite the higher intake of folic acid in the AG, it did not exert influence in the physical performance (43).

Omega-3, an essential fatty acid, must be obtained through diet. Its role as an antioxidant and anti-inflammatory agent is well established. Omega-3 supplementation (2 g or more per day) improves performance in gait speed tests and the TUG, as well as moderately increases muscle mass (44). Omega-3 is a type of PUFA, and in our study, PUFAs were positively correlated with TLM. The intake of omega-3 in this study was assessed based only on diet rather than supplementation and remains to be proved whether supplementation could potentially improve physical performance and muscle strength in patients with acromegaly (44). The consumption of trans fats was nearly four times greater in AG compared to CG. This type of fat, associated with a 34% increase in the risk of all-cause mortality, is known to induce inflammatory and oxidative stress (45). Studies evaluating the effects of trans fats on physical performance and muscle strength have been primarily conducted in animal models. Liou et al., 2013 (46) observed a significant reduction in grip strength in mice fed with a high trans-fat diet compared to those with low consumption. Similarly, Jeyakumar et al. (11) reported that in female rats, trans fat intake reduced insulin-stimulated glucose uptake in muscle, impairing energy production and muscle function. These findings suggest that the high consumption of trans fats in individuals of the AG may have negatively impacted their body composition and muscle strength.

Beta-carotene, a precursor of vitamin A, has been associated with an increase in strength and performance, as shown in the Framingham Offspring study, which revealed that a higher intake of total carotenoids was associated with increased grip strength and a higher walking speed in adults, highlighting the possible role of antioxidants in preserving muscle functionality (47). In our study, beta carotene intake was approximately three times higher in the AG compared to the CG but had no influence in functionality. High concentrations of selenium, a trace element, were associated with lower impairment of limb performance, muscle weakness, and mobility in older adults (48) and with better grip strength in adults without chronic

diseases (39). In our study, HGS, SPPB, and TLM were positively correlated with selenium. HGS was similar between groups, suggesting that selenium may have contributed to leveling the performance of the AG with the CG in this strength test. Similarly, TLM, which was higher in the AG, may also reflect the influence of selenium. However, this element did not appear to significantly impact performance as assessed by the SPPB in the AG, as the score was lower compared to the CG.

Although the AG showed a higher consumption of some nutrients compared to the CG, the FFQ revealed that most participants did not meet the daily recommendations for various micronutrients, such as vitamins and minerals, which are crucial for maintaining health and physical performance. The small sample size, the heterogeneity of the acromegaly group, and the cross-sectional design of the study limit the generalizability of our findings and the ability to infer causality. Additionally, the potential effects of dietary supplements and medications on body composition and muscle strength were not assessed, which have the potential to modify our results. A strength of our study lies in its innovative approach to exploring the dietary intake of individuals with acromegaly and its potential associations with body composition and muscle functionality, areas that are important but remain underexplored in the management of this condition.

CONCLUSIONS

In summary, our results highlight the complexity of the interaction between nutritional intake and body changes in patients with acromegaly. Some nutrients, such as selenium, β-carotene, flavonoids, vitamin E, and niacin, affected physical performance of these patients, as well as muscle strength. However, despite the greater consumption of various beneficial elements, it did not translate into improved physical performance and muscle strength.

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4. DISCUSSÃO

Esta dissertação avaliou, de forma integrada, o impacto da qualidade alimentar na saúde musculoesquelética de indivíduos com acromegalia, considerando tanto a densidade mineral óssea (DMO) quanto a função muscular.

O primeiro estudo destacou que, apesar de não haver diferenças significativas na média da DMO entre os grupos, exceto na região do colo do fêmur em homens com acromegalia, a qualidade óssea foi substancialmente comprometida, com menor TBS e maior prevalência de fraturas totais em indivíduos com acromegalia. Esse achado reflete a complexidade da interação entre os nutrientes e os efeitos do excesso de GH e IGF-I no metabolismo ósseo. Embora o grupo acromegalia apresentasse maior ingestão de nutrientes potencialmente protetores, como vitaminas B1, B9, C e β-caroteno, esses benefícios não foram insuficientes para prevenir a deterioração da qualidade óssea. A ingestão inadequada de cálcio, vitamina D, magnésio e potássio em ambos os grupos pode ter contribuído para a similaridade nos valores de DMO.

As análises de correlação mostraram que o consumo de compostos bioativos, gorduras de boa qualidade, vitaminas e minerais esteve associado a melhores indicadores de TBS e menor ocorrência de fraturas. No entanto, fatores fisiopatológicos específicos da acromegalia, como o desequilíbrio hormonal, parecem atenuar esses benefícios, evidenciando a necessidade de intervenções nutricionais mais direcionadas.

O segundo estudo examinou o impacto da alimentação no desempenho físico e na composição muscular, demonstrando que, embora os pacientes com acromegalia apresentassem maior massa magra total (MMT), atribuída aos efeitos anabólicos do GH e IGF-I, isso não se traduziu em melhor desempenho funcional. Esses pacientes apresentaram pior desempenho na maioria dos testes físicos, exceto na força de preensão palmar (FPP). A associação entre nutrientes como selênio, PUFA, proteínas e ferro com a MMT indica um papel relevante da alimentação na manutenção da composição muscular. Entretanto, o desempenho funcional, medido por testes como TUG e SPPB, foi influenciado por antioxidantes e compostos bioativos, incluindo β-caroteno, flavona, vitamina E e niacina. Esses resultados sugerem que a ingestão adequada desses nutrientes pode mitigar, em parte, as limitações funcionais impostas pela acromegalia.

De maneira integrada, os resultados demonstraram que nutrientes como selênio, β-caroteno e flavonóis exercem papel importante tanto na qualidade óssea quanto na função muscular. Esse efeito combinado reforça a necessidade de uma abordagem nutricional equilibrada e específica para promover a integridade estrutural e funcional do sistema musculoesquelético em pacientes com acromegalia. Apesar das limitações impostas pela doença, estratégias nutricionais adequadas têm o potencial de prevenir ou minimizar alterações musculoesqueléticas ao longo do tempo. Portanto, a ingestão de alimentos ricos nesses nutrientes essenciais para a saúde musculoesquelética, desempenha um papel fundamental na manutenção da integridade óssea e muscular. Dentre esses alimentos, a castanha-do-pará destaca-se como uma fonte significativa de selênio. Alimentos de coloração amarelo alaranjada, como cenoura, mamão, tomate (SCHWEIGGERT et al., 2014) e abóbora (NINČEVIĆ et al., 2023), são ricos em betacaroteno, um importante antioxidante. No grupo dos flavonóis, destacam-se frutas como morango, mirtilo e amora, enquanto entre os vegetais, o espinafre e a couve-flor são fontes relevantes desse composto bioativo. Além disso, o tomate e seus derivados também apresentam quantidades expressivas de flavonóis (MIKULIC-PETKOVSEK et al., 2012; SULTANA & ANWAR, 2008; STEWART et al., 2000). Por fim, a associação entre dieta e saúde musculoesquelética em indivíduos com acromegalia ressalta a importância de um tratamento multiprofissional. Abordagens integradas podem oferecer maior funcionalidade, qualidade de vida e bem-estar, além de reduzir a morbimortalidade nesse grupo.

5. CONCLUSÃO

Em conclusão, indivíduos com acromegalia apresentaram baixa qualidade óssea e maior prevalência de fraturas, mesmo com massa óssea adequada avaliada pela DXA. Esses resultados refletem a complexidade da interação entre o consumo nutricional e as alterações corporais características dessa condição. A ingestão insuficiente de compostos com propriedades antioxidantes e anti-inflamatórias, associada ao consumo excessivo de gorduras trans e carboidratos de baixa qualidade, pode ter contribuído tanto para a deterioração da qualidade óssea quanto para o desempenho físico reduzido. Embora nutrientes como selênio, β-caroteno, flavonoides, vitamina E e niacina tenham demonstrado um impacto positivo no desempenho físico e na força muscular, o maior consumo de elementos benéficos

não foi suficiente para reverter os prejuízos observados, evidenciando os desafios multifacetados que a acromegalia impõe à saúde musculoesquelética.

5.1 RECOMENDAÇÕES PARA TRABALHOS FUTUROS

Em decorrência deste trabalho ser o único estudo até o presente momento avaliando a qualidade alimentar e sua influência no sistema musculoesquelético em pacientes com acromegalia, mais estudos são necessários, como estudos longitudinais os quais possam avaliar a progressão da acromegalia e os efeitos de diferentes intervenções nutricionais ao longo do tempo, favorecendo assim o desenvolvimento de estratégias e protocolos para esse público.

Além dos artigos elaborados ao longo deste trabalho, planejamos um terceiro artigo, o qual irá avaliar o Índice Inflamatório da Dieta (IID) em pacientes com acromegalia, a fim de observar se uma dieta com potencial pró-inflamatório poderia influenciar no sistema musculoesquelético e na ocorrência de mais doenças crônicas em pacientes com a doença.

APRESENTAÇÃO DO MATERIAL DA DISSERTAÇÃO EM CONGRESSOS

Os seguintes pôsteres foram apresentados durante o período do Mestrado:

- Congresso Brasileiro de Atualização em Endocrinologia e Metabologia (CBAEM), realizado em João Pessoa-PB em 2023, intitulados:

“Correlação entre ingestão de nutrientes e avaliação de força muscular e desempenho físico em pacientes com acromegalia” e “Correlação entre ingestão de nutrientes e qualidade óssea em pacientes com acromegalia”.

- Simpósio de Neuroendocrinologia (SINE), realizado em Foz do Iguaçu-PR, no ano de 2023: “*The Dietary Inflammatory Index (DII®) and Its impact on disease control and body composition in individuals with acromegaly*” foi apresentado no

- ENDO2024:

“*Nutrient Intake and Physical Performance Evaluation in Patients with Acromegaly*” em Boston-MA com publicação do resumo no *Journal of the Endocrine Society.*

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APÊNDICE 1 – TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Nós, Victoria Zeghbi Cochenski Borba (Professora de Endocrinologia do departamento de Clínica Médica), Cesar Luiz Boguszewski (Professor de Endocrinologia do departamento de Clínica Médica, Tatiana Munhoz da Rocha Lemos Costa (Médica Endocrinologista e aluna do programa de pós-graduação), Natália Nachbar Hupalowski (nutricionista e aluna do programa de pós-graduação), Cláudia Sanches (médica endocrinologista e aluna do programa de pós-graduação), pesquisadores da Universidade Federal do Paraná, estamos convidando (o Senhor, a Senhora) com diagnóstico de acromegalia a participar de um estudo intitulado "Avaliação do sistema musculoesquelético na Acromegalia". Essa pesquisa é importante para identificar possíveis alterações ósseas e musculares nos pacientes com acromegalia e assim poder preveni-las e tratá-las.

a) O objetivo desta pesquisa é avaliar a função muscular (força e desempenho físico) e a presença de alterações de massa óssea e fraturas nos pacientes com acromegalia em acompanhamento no Serviço de Endocrinologia e Metabologia do Hospital de Clínicas do Estado do Paraná (SEMPR), a fim de melhorar o planejamento do tratamento e auxiliar a implementar medidas de prevenção para evitarem-se quedas e fraturas.

b) Caso o(a) Senhor(a) concorde em participar da pesquisa, será necessário que através da assinatura deste termo autorize o acesso ao seu prontuário, onde serão recolhidos dados referentes à doença e sua respectiva evolução. Além disso, o(a) senhor(a) precisará responder a alguns questionários que serão de extrema importância para a nossa pesquisa. Os questionários farão perguntas sobre sinais e sintomas da sua doença, presença de outras doenças, tratamentos já utilizados, sobre exposição solar, atividade física, hábitos de vida, história pessoal e familiar de fraturas, qualidade de vida e sobre ingestão alimentar. Após responder aos questionários o(a) senhor(a) será encaminhado para avaliação física: serão aferidos o peso, altura, realizado teste de força muscular (preensão palmar), teste de equilíbrio e de

velocidade da marcha (caminhar por 4 metros) e teste de levantar e sentar da cadeira por 5 vezes. Na mesma ocasião ou em uma data agendada posteriormente, será realizada coleta de exames de sangue e de imagem (densitometria mineral óssea de corpo total e ultrassom muscular de perna). As avaliações periódicas serão realizadas posteriormente a cada 2 ou 3 anos com os mesmos exames e testes.

c) Para tanto (o Senhor, a Senhora) deverá permanecer após a sua consulta no Serviço de Endocrinologia e Metabologia do Hospital de Clínicas do Paraná (SEMPR) para responder os questionários, realizar os testes físicos e exames o que levará aproximadamente uma hora e trinta minutos. Caso não seja possível a realização de todos os exames no mesmo dia será agendada uma data posterior para o(a) senhor(a) comparecer no Serviço de Endocrinologia e Metabologia do Hospital de Clínicas do Paraná (SEMPR) para a coleta de exame de sangue e realização dos exames de imagem com duração de aproximadamente uma hora. Caso seja necessário esse retorno em uma data posterior, o deslocamento até o SEMPR não será reembolsado, ficando o transporte por conta do participante do estudo.

d) Com os questionários pode haver algum constrangimento por parte do(a) senhor(a) na hora de respondê-los, tendo em vista que serão pessoas diferentes que colherão os dados necessários ao estudo. E o(a) senhor(a) poderá escolher a qualquer momento não responder a alguma questão. O (a) senhor(a) pode durante os testes físicos sentir um pouco de tontura, cansaço, falta de ar ou queda, caso isso ocorra a avaliação será imediatamente interrompida e será realizado atendimento pela nossa equipe. É possível também que o(a) senhor(a) sinta algum desconforto com a agulhada na coleta do exame de sangue, pode ocorrer dor e um leve hematoma após essa coleta. É importante ressaltar que o risco em relação a radiação proveniente da densitometria óssea é mínimo, e comparável a exposição solar. E que o exame de ultrassonografia muscular pode causar um desconforto pela necessidade de exposição do membro inferior examinado.

e) Alguns riscos relacionados ao estudo podem ser: os dados presentes em seu prontuário podem ser expostos para demais pessoas que não façam parte da pesquisa, pode haver perda de documentos ao longo do estudo. Riscos de constrangimento nas respostas dos questionários, de queda durantes os testes de equilíbrio e de desempenho físico e risco de dor ou sangramento na coleta do exame de sangue.

Os riscos serão evitados ou minimizados: garantindo pela equipe de pesquisa um local reservado para responder aos questionamentos solicitados pelo protocolo de pesquisa, liberdade para não responder questões constrangedoras e limitar o acesso aos prontuários apenas pelo tempo, quantidade e qualidade das informações específicas para a pesquisa. Os testes e exames serão realizados por profissionais capacitados e treinados, realizados em local reservado para evitar possíveis constrangimentos; em caso de tontura, cansaço, falta de ar ou queda, o participante deixará de realizar o procedimento, e será devidamente assistido pela equipe profissional.

Na coleta do exame de sangue os pesquisadores garantem que a coleta será realizada seguindo as recomendações da Sociedade Brasileira de Patologia Clínica/Medicina Laboratorial para Coleta de Sangue Venoso. Será garantido o correto manuseio dos materiais e equipamentos utilizados para o procedimento, ao conhecimento do profissional que realiza a coleta, ao uso de equipamentos de proteção individual (luvas e máscara). Garante que o profissional fará a correta assepsia (lavagem de mãos, assepsia antes da punção com etanol 70%). No caso de sangramentos serão aplicadas técnicas de compressão asséptica e utilização de produtos cicatrizantes adequados, sendo realizado por profissional capacitado e treinado. Haverá suspensão imediata da coleta caso o participante se sinta mal e assegura que a equipe de coleta de amostras biológicas executora do procedimento, está treinada para atender o participante de maneira segura e imediata

f) Os benefícios esperados com essa pesquisa são: conhecendo melhor possíveis alterações ósseas e musculares nos pacientes com acromegalia, conseguiremos ter um melhor planejamento em relação a prevenção e tratamento para evitar quedas e fraturas nesta população, diminuindo os

custos com o tratamento, embora nem sempre (o Senhor, a Senhora) seja diretamente beneficiado(a) por sua participação neste estudo.

g) Os pesquisadores Victória Zeghbi Cochenski Borba, César Luiz Boguszewski, Tatiana Munhoz da Rocha Lemos Costa, Natália Nachbar Hupalowski, Claudia Pinheiro Sanches Rocha, responsáveis por este estudo, poderão ser localizados na Avenida Agostinho Leão Júnior, 285; telefone 2141-1730; e-mails: vzcborba@gmail.com, clbogus@gmail.com, tatimrlemos@yahoo.com.br, natalia.hupalowski@hotmail.com,claudiapsanches@hotmail.com, para esclarecer eventuais dúvidas que (o Senhor, a Senhora) possa ter e fornecer-lhe as informações que queira, antes, durante ou depois de encerrado o estudo por e-mail, telefone em horário comercial, das 9h as 18h. Em situações de emergência ou urgência, relacionadas à pesquisa, os mesmos poderão ser contatados pelo telefone (41)999216206 (Dra Tatiana)

h) A sua participação neste estudo é voluntária e se (o Senhor, a Senhora) não quiser mais fazer parte da pesquisa, poderá desistir a qualquer momento e solicitar que lhe devolvam este Termo de Consentimento Livre e Esclarecido assinado.

i) O material obtido (questionários e dados do prontuário) será utilizado unicamente para esta pesquisa e será destruído ou descartado ao término do estudo, dentro de 5 anos. A qualquer momento o(a) senhor(a) pode solicitar a destruição das amostras de sangue coletadas e armazenadas.

l) As informações relacionadas ao estudo poderão ser conhecidas por pessoas autorizadas: Victória Zeghbi Cochenski Borba, Cesar Luiz Boguszewski, Tatiana Munhoz da Rocha Lemos Costa, Natália Nachbar Hupalowski, Cláudia Sanches, Carolina Aguiar Moreira, Renata Pinheiro. No entanto, se qualquer informação for divulgada em relatório ou publicação, será feito sob forma codificada, para que a **sua identidade seja preservada e seja mantida a confidencialidade.**

m) O(a) senhor(a) terá a garantia de que quando os dados/resultados obtidos com este estudo forem publicados, não aparecerá seu nome, a menos que seja seu desejo ter sua identidade revelada.

( ) Permito a revelação da minha identidade na publicação dos resultados da pesquisa;

( ) Não permito a revelação da minha identidade na publicação dos resultados da pesquisa ;

n) As despesas necessárias para a realização da pesquisa não são de sua responsabilidade e (o Senhor, a Senhora) não receberá qualquer valor em dinheiro pela sua participação.

o) Quando os resultados forem publicados, não aparecerá seu nome, e sim um código.

p) Se o(a) senhor(a) tiver dúvidas sobre seus direitos como participante de pesquisa, você pode contatar também o Comitê de Ética em Pesquisa em Seres Humanos (CEP/SD) do Setor de Ciências da Saúde da Universidade Federal do Paraná, pelo e-mail cometica.saude@ufpr.br e/ou telefone 41 - 3360-7259, das 08:30h às 11:00h e das 14:00h.às 16:00h. O Comitê de Ética em Pesquisa é um órgão colegiado multi e transdisciplinar, independente, que existe nas instituições que realizam pesquisa envolvendo seres humanos no Brasil e foi criado com o objetivo de proteger os participantes de pesquisa, em sua integridade e dignidade, e assegurar que as pesquisas sejam desenvolvidas dentro de padrões éticos (Resolução nº 466/12 Conselho Nacional de Saúde).

Eu, _____ li esse Termo de Consentimento e compreendi a natureza e o objetivo do estudo do qual concordei em participar. A explicação que recebi menciona os riscos e benefícios. Eu entendi que sou livre para interromper minha participação a qualquer momento sem justificar minha decisão e

sem qualquer prejuízo para mim. Fui informado que serei atendido sem custos para mim se eu apresentar algum dos problemas relacionados no item e].

Eu concordo, voluntariamente, em participar deste estudo.

Curitiba, ___ de _____ de _____

Assinatura do Participante de Pesquisa ou Responsável Legal

Eu declaro ter apresentado o estudo, explicado seus objetivos, natureza, riscos e benefícios e ter respondido da melhor forma possível às questões formuladas.

_____

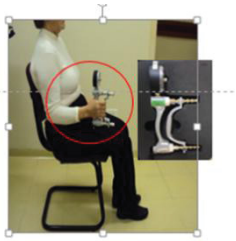
Assinatura do Pesquisador Responsável ou quem aplicou o TCLE

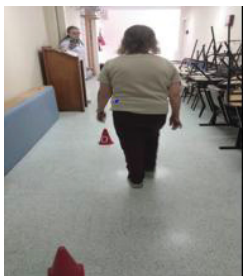
APÊNDICE 2 – LAUDO FÍSICO-FUNCIONAL E ÓSSEO ENTREGUE AOS PARTICIPANTES DO PROJETO ACROSSO

Laudo de Densidade Mineral Óssea e avaliação físico-funcional

Projeto ACROSSO

Nome: **Idade:**

AVALIAÇÃO DA DENSIDADE MINERAL ÓSSEA				
Avaliação	**Objetivo do teste**	**Data/Valor obtido**	**Valores de referência**	**Conclusão**
Densitometria do Colo de Fêmur, fêmur total e coluna	Verificar o diagnóstico de Osteoporose e Osteopenia	Data: DMO colo: DMO fêmur: DMO lombar:	Normal = T-score igual ou superior a - 1,0 SD; Osteopenia = T-score entre -1,0 e -2,49 SD; Osteoporose = T-score igual ou inferior a -2,5 SD. (1)	
TRIAGEM DE SARCOPENIA				
Avaliação	**Objetivo do teste**	**Data/Valor obtido**	**Valores de referência**	**Conclusão**
FPM  (Kg)	Avaliar a força muscular		< 27 Kg (5) (homens) < 16kg (mulheres) Provável Sarcopenia	
Teste de sentar-se e levantar 5 vezes (seg) 	Avaliar a força de membros inferiores (“pernas”)		>15s Provável Sarcopenia (5)	
TUG (segundos)	Avaliar a		≥ 20 s	

	mobilidade funcional e o risco de sarcopenia		Sarcopenia [5]	
Velocidade da marcha 4 metros 	Avaliar a velocidade da caminhada		≤0,8m/s Sarcopenia [5]	
Conclusão[5]	( ) Não sarcopênico ( ) Provável sarcopenia ( ) Sarcopenia ( ) Sarcopenia severa			
AVALIAÇÃO DO RISCO DE QUEDAS				
TUG (segundos) 	Avaliar a mobilidade funcional e o risco de quedas		Risco de Quedas 60- 69 anos: 8,1 s 70-79 anos: 9,2 s 80-99 anos: 11,3 s [6]	( ) Sem risco de queda ( ) Risco de queda

Dúvidas contatar Claudia Pinheiro Sanches ou Natália Nachbar Hupalowski
E-mails: claudiapsanches@hotmail.com ou natalia.hupalowski@hotmail.com
Telefone: (41) 99912-7219 (Cláudia) ou (41) 99904-9151 (Natália)

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EQUIPE DO PROJETO	
Mestrandas do Programa de Pós-Graduação em Medicina Interna e Ciências da Saúde Cláudia Pinheiro Sanches Natália Nachbar Hupalowski	Orientadora do projeto Prof.ª Dr.ªVictória Zeghbi Cochenski Borba Coorientador do projeto Profº. Dr. Cesar Boguszewski

ANEXO 1 – SUBMISSÃO AO CEP DO PROJETO ACROSSO

HOSPITAL DE CLÍNICAS DA UNIVERSIDADE FEDERAL DO PARANÁ - HCUFPR

Plataforma Brasil

COMPROVANTE DE ENVIO DO PROJETO

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação do sistema musculoesquelético na acromegalia

Pesquisador: Victoria Zeghbi Cochenski Borba

Versão: 2

CAAE: 49629321.7.0000.0096

Instituição Proponente: Hospital de Clínicas da Universidade Federal do Paraná

DADOS DO COMPROVANTE

Número do Comprovante: 078689/2021

Patrocinador Principal: Financiamento Próprio

Informamos que o projeto Avaliação do sistema musculoesquelético na acromegalia que tem como pesquisador responsável Victoria Zeghbi Cochenski Borba, foi recebido para análise ética no CEP Hospital de Clínicas da Universidade Federal do Paraná - HCUFPR em 15/07/2021 às 09:41.

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